ORIGINAL RESEARCH

Menstrual Cycle Changes after COVID-19 Infection: Does Coronavirus-induced Stress Lead to Hormonal Change?

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Abstract

Background: Pieces of clinical evidence suggest that coronavirus disease-2019 (COVID-19) viral infection results in hormonal imbalance leading to changes in menstrual cycles of women. This study has been conducted with the aim to determine the effect of COVID-19 infection and its vaccine on menstrual cycle patterns.

Materials and methods: This was a cross-sectional study to observe any changes in menstrual cycle after COVID-19 infection or after its vaccination. A Web Link collector generated the survey's universal resource locator (URL) and was sent via social media messages to females in the general population as well as healthcare workers.

Results: Menstrual cycles remained unaltered in 154/228 (67.5%) of women post-COVID-19 infection irrespective of its severity. Out of 228, one-third of women, i.e., 74/228 (33%), reported changes in their menstrual patterns, with respect to either cycle length, duration of flow, number of pads used, pain during menses, or premenstrual symptoms (PMSs). Menstrual blood loss was decreased by 14% (32/228) and 18%; 42 women complained of increased flow during menses. Twenty percent of women who had severe infections had menorrhagia. Out of the 590 women who completed the questionnaire, 436 (73.8%) were vaccinated against COVID-19 and 154 (26%) were unvaccinated. After vaccination, 290/436 around one-third of women (66.5%) had normal menstrual cycle, 21 women (4.8%) had decreased menstrual blood flow, and 18 women (4.1%) reported increased menstrual flow.

Conclusion: COVID-19 infection affected the menstrual cycle of only one-third of women and this effect was temporary. This effect might be due to stress and anxiety affecting the hypothalamic-pituitary axis (HPA). More studies are needed to support this effect.

Keywords: Coronavirus, Coronavirus disease-2019 and menstrual cycle, Coronavirus and menstrual cycle, Severe acute respiratory syndrome coronavirus 2 and hormonal change, Women psychological health.

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Introduction

The fear of novel coronavirus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent of severe acute respiratory syndrome, is the latest threat looming over the world.[1,2] The coronavirus disease-2019 (COVID-19) pandemic took a toll on the mental health of people due to loneliness, social isolation, and financial constraints. It leads to anxiety and fear of contracting the disease among all ages and population.[3] About one-third of the people reported stress, anxiety, and depression during COVID-19 pandemic.[4]

Psychological stress can alter the menstrual cycles. Stress, even without any organic cause, can activate the hypothalamic-pituitary–ovarian axis altering the release of gonadotropin-releasing hormone (GnRH) leading to functional hypothalamic amenorrhea (FHA) and chronic anovulation.[5]

Pieces of clinical evidence suggest that COVID-19 viral infection results in hormonal imbalance leading to changes in menstrual cycles in women of childbearing age. This study has been conducted with the aim to determine the effect of COVID-19 infection and its vaccine on menstrual cycle patterns.

Materials and Methods

This was a cross-sectional study to observe any changes in menstrual cycle after COVID-19 infection or after its vaccination.

Inclusion criteria in the study were as follows:

- Age between 18 and 45 years,
- History of regular periods during the 6 months preceding the pandemic,
- Willing to participate in the study.

Those with history of irregular periods were excluded from the study.

A Web Link collector generated the survey URL through which respondents could access the survey and send their answers. For its distribution, a convenient, non-probability sampling method was adopted. The URL was sent via social media messages to the females in general population as well as healthcare workers. Recipients were free to fill in the questionnaire and were asked to forward the link

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to others, without communicating back their list of addressees. The questionnaire was composed of nine closed questions in the local language. Respondents were asked to provide honest answers, were not given any incentives for participation, and could reply only once to the survey.

Information related to menstrual history was obtained over a questionnaire in the local language (Table 1).

Important definitions used to assess menstrual abnormality were as follows:

- Normal menstrual cycle—menstruation occurs at intervals of 24–38 days, with a duration of 4–8 days and normal flow.
- Amenorrhea—absence of menstruation for >90 days.
- Prolonged cycle duration—lasting >8 days.
- Short cycle duration—lasting <4 days.
- Infrequent cycle—menstruation occurring >38 and <90 days.
- Frequent cycles—menstruation occurring <24 days.
- Heavy bleeding—compared to her previous cycles.
- Scanty bleeding—compared to her previous cycles.

Results

In this study, 590 women filled out the questionnaire. Out of the 590 cases, 249 were COVID-19-positive and remaining 341 were COVID-19-negative.

Figure 1 demonstrate the general properties of Chi-square distributions. Figures 1A, D and G clearly demonstrate that as the degree of freedom increases, the distribution becomes more symmetric and the entire curve moves toward the right and the variability increases. Figures 1B and F show Chi-square distribution with degrees of freedom (3) and an upper bell-shaped curve sloping toward the left. Figures 1B and F also show that the upper tail for a Chi-square distribution with 5 and 7, respectively, degrees of freedom and a cutoff of 5.1 and 7.1, respectively, in the shaded area of the curve. This normal distribution is showing the validation of hypothesis using two factorial (*fx*) scheme. Figure 1C demonstrates the left-tailed χ^2 distribution with non-negative and non-symmetric characteristics that is proving the hypothesis and does not lie in rejection region. Figure 1E shows right-tailed χ^2 distribution with non-negative and non-symmetric distribution that demonstrates less than the critical value and it is not in rejection region.

Table 1: Questionnaire used in Web Link collector

Characteristics	χ^2 *SD* *p*	*N (%)*
Did you have COVID-19 infection recently?	15.195 1 0.000***	249 (42.06)
Age (years)		
15–24	14.961	11
25–39	1	101
40–50	0.002**	116
>50		
Are your menstrual cycles normal as before COVID-19 infection?	0.867 1 0.648	402 (69.31)
Did you get your COVID-19 vaccine?	9.345 1 0.002**	427 (73.62)
Did you had heavy flow in menstrual cycle after COVID-19?	15.708 1 0.000***	337 (58.10)
Did you get your menstrual cycles earlier after COVID-19 infection?	6.261 1 0.100	44 (7.5)
Did you get hospitalized due to COVID-19 infection?	7.111 1 0.007**	26 (4.48)

Chi-square analysis of descriptive variables; The Chi-square comparison for all descriptive variables were made with Q1 (Did you have COVID-19 infection?); SD, standard deviation; *p <0.05; **p <0.01; and ***p <0.001

COVID-19 cases were further distributed according to their age and severity of the disease. Twenty-four women had severe infection requiring hospitalization. Among the age group 10–25 years, 4 cases had severe infection and required hospitalization; in the age group 26–39 years, 11 women had severe COVID-19; and in the age group 40–55, 9 women had severe disease; rest all had mild infection only.

Among 249 cases, before acquiring COVID-19 infection menstrual cycles were regular in 176 cases (71%) and irregular in 52 women (21%). Around 19 cases had already attained menopause and two had secondary amenorrhea, so they were excluded from result analysis.

Menstrual cycle remained unaltered in 154/228 (67.5%) women post-COVID irrespective of COVID severity. Out of 228, 74 (32.5%) women reported changes in their menstrual patterns, with respect to either cycle length, duration of flow, number of pads used, pain during menses, or PMS (Figs 1 and 2). Periods were delayed in 18.5% (42/228) women. Out of these 74 cases, 32 cases complained of decreased flow and 42 cases complained of increased flow during menses (Fig. 3). A woman who required oxygen for 12 days developed significant hirsutism post-recovery.

Dysmenorrhea developed as a new symptom in 11 patients (1.9%) of mild COVID-19 and 1 patient (4.1%) of moderate-to-severe COVID-19. Majority of the patients experienced no change in pain during menstruation.

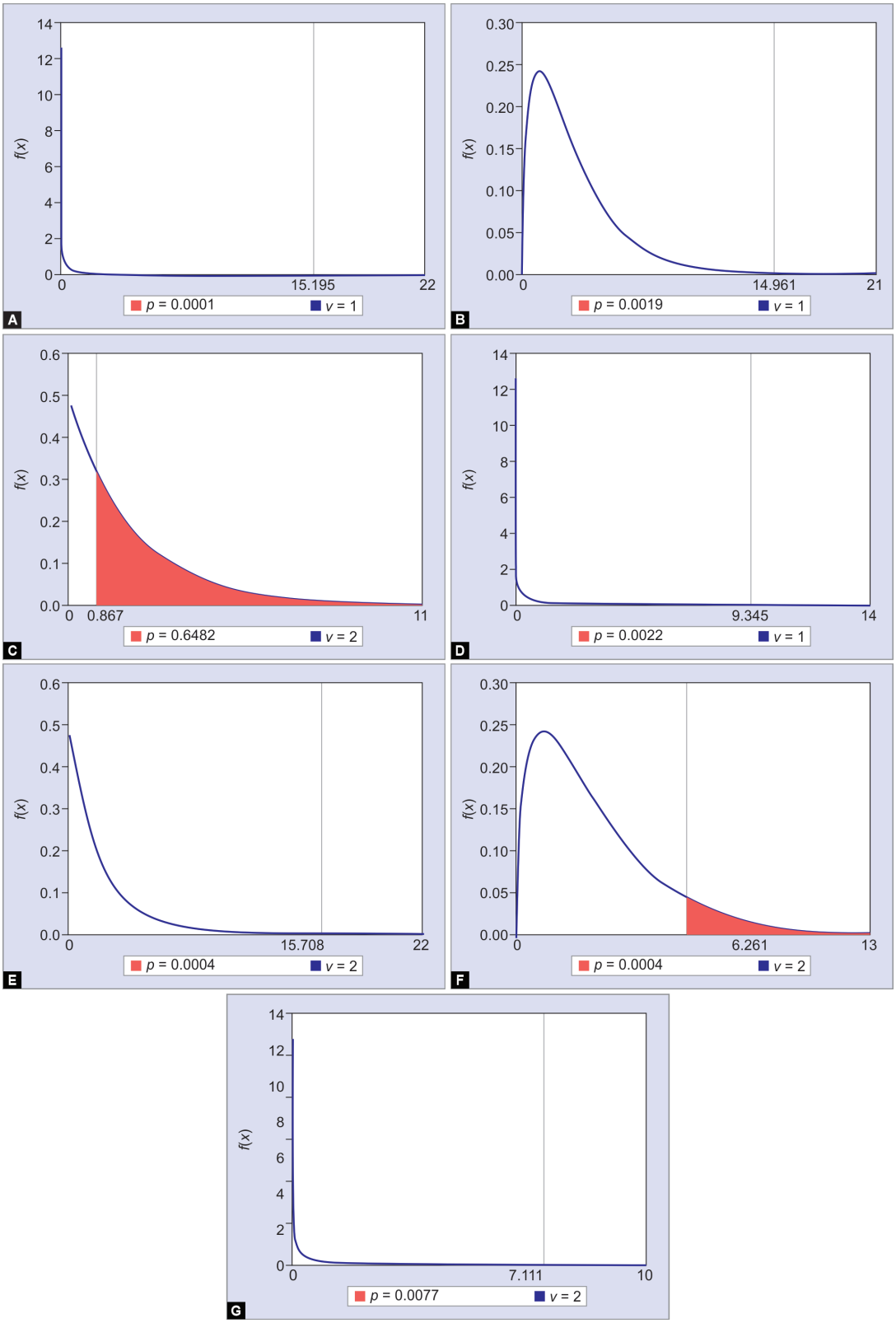
Similarly, most of the patients did not perceive any change in PMSs. Patients with moderate-to-severe disease experienced more change in PMS (7%) as compared to those with mild disease (3%), but both these menstrual parameters were not statistically significant in relation to disease severity.

Sexual health was assessed by the women's desire for sexual activity and around 4% of the cases reported hypoactive sexual desire.

In this study, the authors also took menstrual history from vaccinated and unvaccinated cases. Out of the 590 cases, 436 (73.8%) were vaccinated and 154 (26%) were unvaccinated. After vaccination, 290 cases (66.5%) had normal menstrual cycle, 21 cases (4.8%) had decreased menstrual blood flow and 18 cases (4.1%) reported increased menstrual flow. Fourteen cases (3.2%) present with decreased interval between menses and 27 cases (6%) had complaint of increased interval between menses (Fig. 4).

Discussion

Psychological stress can lead to secondary amenorrhea but also worsening of symptoms associated with menstruation. Even high stress,[6] emotional instability, and depression[7] can lead to dysmenorrhea. Premenstrual symptoms (PMSs) and menorrhagia have their links with psychological distress.[8,9] Evidence favors association of stress with lower libido in women.[10]



Figs 1A to G: The figure showing Chi-square distribution of descriptive analysis (A) Did you have fever, cough, and sneezing symptoms recently?; (B) Age; (C) Did the menstrual cycle is normal as before COVID-19 infection?; (D) Did you get your COVID-19 vaccine?; (E) Did you have more events of menstrual cycle after COVID-19?; (F) Did you have menstrual cycle event earlier after COVID-19 infection? and (G) Did you get hospitalized due to COVID-19 infection?

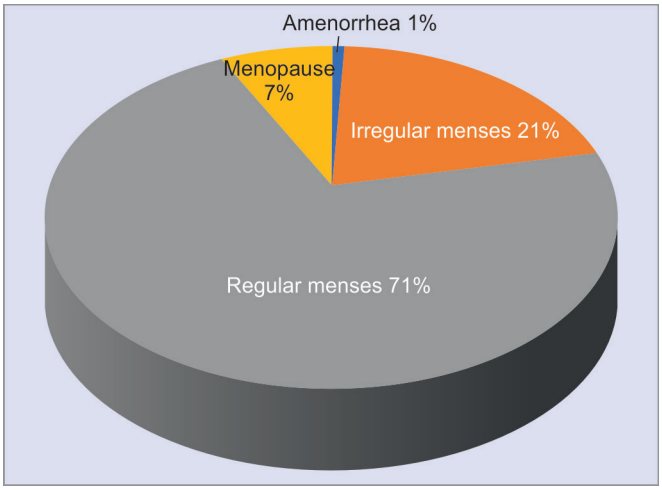


Fig. 2: Pre-COVID-19 menstrual cycle pattern

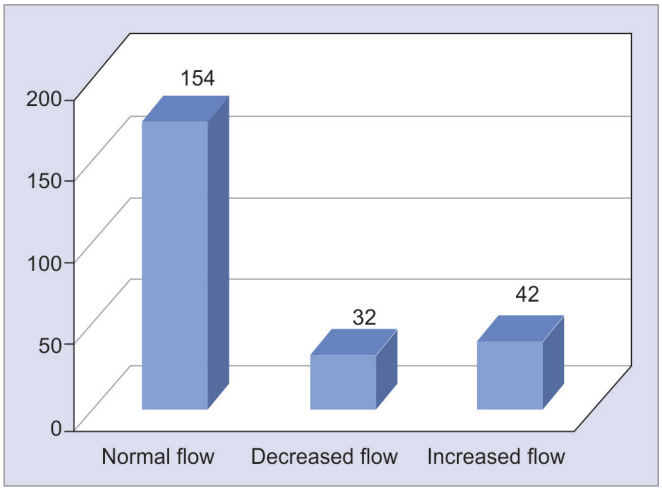


Fig. 3: Changes in menstrual pattern after COVID-19 infection

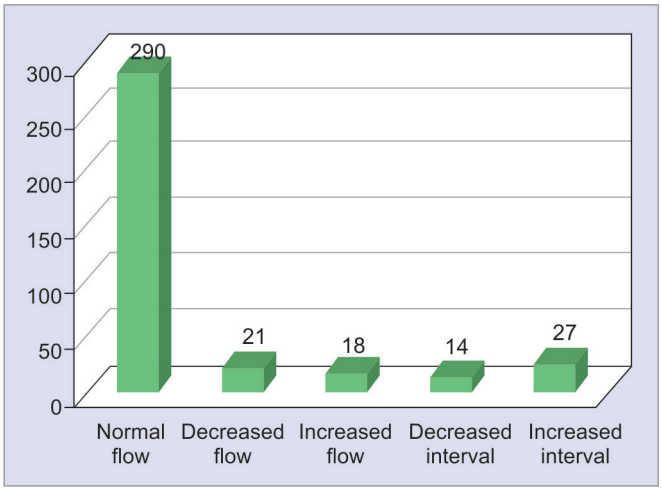


Fig. 4: Changes in menstrual pattern in vaccinated cases

Figure 1 demonstrate the general properties of Chi-square distributions. Figures 1A, D and G clearly demonstrate that as the degree of freedom increases, the distribution becomes more symmetric and the entire curve moves toward the right and the variability increases. Figures 1B and F show Chi-square distribution with degrees of freedom (3) and an upper bell shape curve sloping toward the left. Figures 1B and F also show that the upper tail for a Chi-square distribution with 5 and 7, respectively, degrees of freedom and a cutoff of 5.1 and 7.1, respectively, in the shaded area of the curve. This normal distribution shows the validation of hypothesis using two factorial (*fx*) schemes. Figure 1C demonstrates the left-tailed χ^2 distribution with non-negative and non-symmetric characteristics that is proving the hypothesis and does not lie in rejection region. Figure 1E shows right-tailed χ^2 distribution with non-negative and non-symmetric distribution that demonstrates less than the critical value and it is not in rejection region.

This study examined the impact of the COVID-19 outbreak on menstrual cycle characteristics. These menstrual irregularities might be attributed to anxiety and fear of losing the near and dear ones during the pandemic. Exposure to stress causes the dysregulation of HPA axis activity due to mechanisms like: (1) the inhibition of hypothalamic GnRH release by corticotrophin releasing hormone (CRH), endogen opioids, and glucocorticoids, (2) decreased pituitary response to GnRH, leading to decreased luteinizing hormone (LH) secretion, (3) direct inhibitory effect of glucocorticoids on the secretion of estrogen and progesterone, (4) glucocorticoid-induced resistance to the gonadal steroids in target tissues, and (5) direct catecholaminergic inhibition on follicle stimulating hormone (FSH), LH, and prolactin secretion.

Results of a similar cross-sectional online survey also found that COVID-19 infection leads to altered menstrual patterns where the length of periods and the number of pads used decreased.[11] They attributed anxiety and stress to the altered patterns. In our study, 32% of women present with irregular menses and most common abnormality is decreased interval between menses or frequent cycles. Out of these, around 95% of cases returned to their normal cycle within 3–4 months of relieving of their symptoms.

Evidence links PMS with stress. A study reported that over 50% of respondents had worsening PMS. However, in the current study, PMS was reported only in 7% of cases.

Limitation of the study was that it was an online survey and direct patient interaction could not be done. The strength of the study was that it was the first study reported from India and abroad and the sample size was good enough. Research is lacking on the effect of novel coronavirus on women's menstrual cycles.

Conclusion

COVID-19 infection affected the menstrual cycles of one-third of women, but this effect was temporary and might be due to stress and anxiety affecting the HPA. More studies are needed to support this effect.

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