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Pathological Effects of COVID-19 on Menstrual Cycle: An Exploratory Study

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ABSTRACT

Background: COVID-19 is linked to multiple health disruptions, such as menstrual disruptions. The patterns of the cycles may be affected by both infection and vaccination. **Objective:** The study aimed to investigate the association between COVID-19 infection, vaccination, and menstrual disturbances. **Study Design:** Cross-sectional study. **Settings:** Khyber Teaching Hospital, Peshawar Pakistan. **Duration:** July to December 2021. **Methods:** 168 female COVID-19 hospitalized patients aged 18-45 years. A questionnaire was used to gather information, which included demographics, details of infection, vaccination history, and menstrual history. The statistical analysis involved descriptive statistical analysis, chi-square, and logistic regression. A p-value of <0.05 was considered statistically significant. **Results:** Out of 168 individuals, 28.57% had COVID-19, and 71.43% were immunized. Infection-related menstrual abnormalities affected 50% of women, with 28.57% experiencing discomfort. 14.29% stopped or missed periods. 45% of subjects reported cycle length alterations, while 42% reported lengthier cycles. 50% of participants said menstrual abnormalities impaired their quality of life socially and psychologically. Treatment with Tranexamic Acid reduced menstrual change length (p = 0.0019). Tranexamic Acid and OCPs were used to address menstruation issues in 62.5% of subjects. These data suggest that COVID-19 infection and immunization may lead to substantial menstrual abnormalities that can be treated. **Conclusion:** COVID-19 infection and immunization are associated with menstrual abnormalities, affecting social and psychological well-being. Menstrual care interventions, such as Tranexamic Acid, mitigate these disturbances, underscoring the need for specialized post-COVID care. Additional investigation is required to comprehend the fundamental mechanics.

Keywords: *COVID-19, Menstrual irregularities, Vaccination impact, Menstrual cycle changes.*

INTRODUCTION

A new coronavirus disease (COVID-19) outbreak occurred in Wuhan, China, in December 2019. Since that time, it has swiftly proliferated globally, resulting in a significant catastrophe impacting public health.[1] The epidemiological study identified Wuhan's Huanan Seafood Wholesale Market as a source, leading to its closure and disinfection, followed by the rigorous pursuit of active case detection.[2] Furthermore, COVID-19 individuals have exhibited multisystem problems alongside respiratory symptoms, including circulatory and digestive system concerns.[3] The virus that causes COVID-19 (SARS-CoV-2) may enter cells through its receptor, ACE2, according to one theory.[4]

A cell-surface receptor for SARS-CoV-2, the angiotensin-converting enzyme to 2-receptor, is widely expressed in the endometrium and female reproductive system. These tissues might be directly affected by the virus.[5] Prior research suggested that COVID-19 infection or immunization affects menstrual periods.[6] The most often documented alterations were irregular menstruation, heightened premenstrual disorder symptoms, increased blood loss, and intermittent menstruation.[7,8]

According to research, the COVID-19 pandemic was significantly associated with higher levels of stress, anxiety, depression, and Post-Traumatic Stress Disorder (PTSD), as well as more severe psychological impacts in women. Psychological strain is known to influence menstruation.[9,10] Menstrual irregularities associated with COVID-19 vaccination were evaluated and documented in a thorough review and meta-analysis, which found statistically significant associations between vaccination and monthly irregularities in women of reproductive age.[11] Extensive research is still underway to understand how COVID-19 impacts the female reproductive system. Menstrual cycle changes may result from SARS-CoV-2 infection's effects on the hypothalamic-pituitary-ovarian-endometrial axis.[12] With severe COVID-19, hypothalamic hypogonadism may appear, which might lead to irregular menstruation and temporary amenorrhea. The ovaries and endometrial tissue are rich in ACE-2 receptors.[13]

Furthermore, post-vaccination for COVID-19 demonstrated significant alterations in menstrual periods. Reported menstrual alterations in several trials varied, including both increased bleeding and the end of menstruation.[14] Historically, women's health has been neglected in scientific studies. Although female volunteers were permitted to participate in clinical research by the National Institutes of Health in 1993, sex is frequently ignored as an experimental criterion.[15] This study aims to examine the relationship between COVID-19 infection, various vaccinations, and irregular menstruation after infection, particularly in female COVID-19 patients who are hospitalized. While a number of studies have assessed the impact of the COVID-19 pandemic and quarantine on women's mental health and menstrual changes, most of them have only examined the general population and have seldom included data on hospitalized women. The results may provide essential guidance for healthcare professionals, enhancing patient care, post-vaccination support, and public health initiatives. The aim was to investigate the relationship between COVID-19 infection, various vaccination types, and menstrual complications occurring post-infection.

METHODS

The cross-sectional study was conducted at Khyber Teaching Hospital from July to December 2021. Ethical approval was obtained from the Institutional Ethical Review Committee (ERC/ERB) vide letter No. [Ref. No. KTH/Gyne/2021/618], dated 25th June 2021. Data were acquired from female COVID-19 patients who were hospitalized. All participants provided informed consent before engaging in the study, and all data were anonymized to safeguard privacy.

Participants were selected from the hospital's isolation and recovery wards, with inclusion criteria restricted to women of reproductive age (18–45 years) who had been hospitalized owing to COVID-19. Women with pre-existing menstrual irregularities unrelated to COVID-19, those who were pregnant, or those who used hormonal contraception were excluded.

A total of 168 patients participated in the study. The sample size was calculated using the formula for cross-sectional studies:

$$n = \frac{Z^2 \times p \times (1-p)}{d^2}$$

where Z = 1.96 at 95% confidence level, p = anticipated prevalence of menstrual symptoms post-vaccination (66.3%), from Muhaidat *et al.,* (2022),[16] and d = margin of error (0.05).

$$n = \frac{(1.96)^2 \times 0.663 \times (1-0.663)}{(0.05)^2} \approx 168$$

Thus, a total of 168 patients participated in the research.

Data were gathered through a standardized questionnaire presented throughout their hospitalization. The questionnaire included demographics, COVID-19 infection specifics, vaccination status, and menstruation history. Participants were requested to disclose any alterations in their menstrual cycle after their COVID-19 infection, including cycle length, duration, volume, and related symptoms.

The data were analyzed using descriptive statistical methods to describe baseline characteristics, with categorical variables expressed as percentages and continuous variables represented as means (standard deviation) or the medians (interquartile range), contingent upon the distribution. Chi-square tests were used for categorical data, while t-tests or non-parametric testing were applied for continuous variables to compare various immunization groups and menstrual changes. The association between COVID-19 infection and irregular menstruation was examined using logistic regression models, which controlled for pertinent variables such as age, body mass index, and type of immunization. A statistically significant p-value was defined as less than 0.05. All statistical analyses were performed with R 4.3.2.[17]

RESULTS

The results were obtained from a sample size of 168 females. A majority of individuals, 69.64% (n=117), reported using hormonal therapy, whilst 71.43% (n=120) claimed that they did not get such treatment. Concerning COVID-19 infection, 28.57% (n=48) of subjects indicated having been infected, while 5.36% (n=9) reported not

contracting the virus. Regarding medicinal intervention in COVID-19 therapy, 91.07% (n=153) of respondents reported using drugs, whilst 8.93% (n=15) did not. Regarding hospital admissions for COVID-19, 1.79% (n=3) were admitted, 12.50% (n=21) were not admitted, and 14.29% (n=24) had missing data. A majority 71.43% (n=120) of individuals were vaccinated against COVID, whilst 28.57% (n=48) were not. Regarding menstrual health, 10.71% (n=18) of participants reported experiencing menstruation issues before receiving the COVID vaccination or contracting the virus, whereas 85.71% (n=144) did not. Additionally, 28.57% (n=48) of participants reported experiencing menstrual discomfort post-infection, while 14.29% (n=24) reported missing periods or discontinuation after the vaccination or infection. Finally, the findings indicated that 50.00% (n=84) of participants felt that monthly abnormalities adversely impacted their social and psychological quality of life, whereas 62.50% (n=105) of respondents sought therapy for menstruation care, as shown in Table 1.

Table 1: Frequency and percentage distribution of key health-related factors, including hormonal treatment, COVID-19 infection, vaccination, and menstrual health, among 168 participants

Variable	Category	Frequency & Percentage
Are you using any hormonal treatment?	Yes	69.64% (n=117)
	No	71.43% (n=120)
Did you get infected with COVID 19	Yes	28.57% (n=48)
	No	5.36% (n=9)
Were there medications used during treatment?	Yes	91.07% (n=153)
	No	8.93% (n=15)
Did you get admitted to the hospital due to COVID?19	Yes	1.79% (n=3)
	No	12.50% (n=21)
	ND	14.29% (n=24)
Did you get the COVID vaccine	Yes	71.43% (n=120)
	No	28.57% (n=48)
Did you suffer any menstrual problems before COVID vaccine infection	Yes	10.71% (n=18)
	No	85.71% (n=144)
	Yes	14.29% (n=24)
Did you experience pain during periods after the infection?	Yes	28.57% (n=48)
Have you missed your period or experienced cessation after COVID COVID-19 vaccine?	Yes	14.29% (n=24)
Did these menstrual irregularities affect your quality of life socially and psychologically	Yes	50.00% (n=84)
Menstrual care treatment	Yes	62.50% (n=105)
Age group	18-25 years	50.00% (n=84)
	26-35 years	37.50% (n=63)
	36-45 years	10.71% (n=16)

The research investigated the correlations among parameters, including age, the quantity of COVID-19 vaccination doses, alterations in the menstrual cycle after COVID infection, and menstrual care interventions. The correlation study demonstrated weak or negligible statistically significant relationships among age, vaccination dosages, and alterations in the menstrual cycle, with p-values over 0.05 signifying the absence of meaningful associations. A substantial negative connection ($p = 0.0019$) was identified between the length of monthly modifications post-COVID and menstrual care therapy, indicating that specific therapies may mitigate extended menstrual alterations after COVID-19 infection. A slight positive connection was identified between age and menstrual care therapy ($p = 0.4564$); however, no significant impact was seen regarding the number of dosages or alterations in menstrual cycle length attributable to infection.

Table 2: Table showing the correlation coefficients and p-values between various factors such as age, COVID-19 vaccine doses, menstrual changes, and menstrual care treatment

Variable	Number of factors	Correlation	P-value
Age	Number of doses	0.1086	0.1612
	After a COVID infection, changes in periods days	-0.0377	0.6278
	Menstrual change duration after COVID	-0.0465	0.5496
	Menstrual care treatment	0.0578	0.4564
Number of doses	After a COVID infection, changes in periods days	0.0648	0.4037
	Menstrual change duration after COVID	-0.0748	0.3355
	Menstrual care treatment	0.0704	0.3642
After the COVID infection, there is a change in days	Menstrual change duration after COVID	0.0836	0.2810
	Menstrual care treatment	0.0122	0.8754
Menstrual change duration after COVID	Menstrual care treatment	-0.2383	0.0019

The dataset comprises 168 records and examines the correlation between COVID-19 immunization, infection, and periods. The most prevalent prior medical conditions are asthma (6 individuals), diabetes and hypertension (3 people each), and deep vein thrombosis (3 participants). Participants reported no use of hormonal therapy, with 120 indicating no use and 48 lacking data. The majority of

individuals (120) did not indicate the use of any hormone therapies. Regarding COVID-19, 153 individuals did not disclose their infection situation, while those who did received treatment with Duphaston (3 instances) or thyroxine (9 cases). A substantial cohort of patients (144) indicated alterations in their period timing after COVID infection, specifically regarding the interval between successive periods, while 24 people reported no alterations. Vaccines given included Pfizer, Sinopharm, and AstraZeneca, with 48 subjects getting two doses. Among the individuals, 42 reported increased elongation of their menstrual periods, while 45 indicated a reduction in cycle length and frequency. Furthermore, 24 people need hospitalization due to significant hemorrhaging, with prescriptions including Tranexamic Acid and oral contraceptive pills. A range of period care interventions was administered, with 105 patients receiving post-COVID menstrual care therapies.

Table 3: Table summarizing the key variables and numerical values related to COVID-19 vaccination, infection, and menstrual health changes in the study population

Variable	Summary and number of individuals
Any previous Medical Illness	Asthma: 6, Diabetes and HTN: 3, DVT: 3
Did you get infected with COVID-19?	Treatment types: Duphaston (3), Thyroxine (9)
Did you get the COVID vaccine?	Common vaccines: Pfizer, Sinopharm
Number of doses	48 participants received two doses
Did you suffer from any menstrual problems before the COVID vaccine/infection?	Many experienced menstrual irregularities
After a COVID infection, did you experience a change in the number of days between two consecutive periods?	Change: 144 participants, No change: 24
If you experienced heavy bleeding, did you require hospital treatment or a visit?	Some required hospital visits for heavy bleeding
Did these menstrual irregularities affect your quality of life socially/psychologically?	45 experienced "became closer and shorter" cycles, 42 experienced "became longer"
Cycle after infection	Most common treatments: IV Tranexamic acid, OCPs, Blood transfusion
Menstrual change duration after COVID-19	Durations varied, ranging from short to long-term

DISCUSSION

This study's results highlight the substantial influence of COVID-19 infection and immunization on menstrual health, a subject that has garnered heightened interest in recent years. The data indicate that a significant percentage of individuals had menstrual abnormalities after illness or immunization. Specifically, 50% of participants said that menstrual abnormalities impacted their social and psychological quality of life. Furthermore, 28.57% had dysmenorrhea post-infection, whilst 14.29% either skipped their menstrual cycles or suffered amenorrhea after vaccination or infection. These alterations often coincided with psychological suffering, illustrating the broader social and emotional repercussions of menstrual abnormalities. Although the physiological reasons driving these changes are not fully understood, the research emphasizes the need to recognize menstrual health as an essential aspect of post-COVID treatment.

This research found that 52.2% (530/1016) of SARS-CoV-infected subjects had alterations in menstruation, surpassing the 16% reported by Khan SM *et al*.[18] Changes in the monthly length, menstrual flow, and menstrual cycle were the most common irregularities. Many studies have examined the relationship between COVID-19-related mental illnesses and changes in menstruation, and they have demonstrated that the virus may affect the female menstrual cycle, which is consistent with our findings.[19,20]

Atypical menstrual cycles following vaccination or sickness were present in 21.7% of cases. However, in 61.9% of instances post-vaccination and 53.8% of cases post-infection, the cycles returned to normal after three cycles, suggesting that the changes were transient. After infection or immunization, there was a substantial increase in dysmenorrhea ($p < 0.001$).[21] After infection, menstrual changes were more noticeable than after immunization; in 14.2% and 19.2% of cases, respectively, a cycle length extension of more than one week was seen. 24.5% reported thrombosis following sickness, whereas 18.5% had it following vaccination.[22]

A potential reason for alterations in menstruation is that it is affected by mental health. Numerous studies have focused on mental health during the COVID-19 pandemic.[23] According to two studies, moderate to severe levels of stress, anxiety, and depression were present in 52.2–62.9%, 58.1–63.6%, and 24.9–58.6% of the study population, respectively.[19] Our research revealed that the majority of female COVID-19 patients experienced alterations in their menstrual cycles after hospitalization and seclusion. These alterations correlate with the length of isolation, hospitalization, and indications of mental health issues. A comparable research indicated that

problems and severe sickness were linked to an extended menstrual cycle.[24,25] A cross-sectional investigation revealed that COVID-19-related elevated stress correlates with substantial alterations in menstrual cycle length, menstrual period duration, and heightened intermenstrual spotting relative to pre-infection levels.[26]

CONCLUSION

This research offers significant insights into the effects of COVID-19 infection and immunization on menstrual health. A considerable percentage of participants had menstrual abnormalities post-COVID-19 infection, with several individuals indicating a detrimental impact on their quality of life, both socially and mentally. Menstrual discomfort and alterations in the cycle were prevalent post-infection, underscoring the need for improved care of these symptoms. A significant proportion of individuals need menstrual care therapies, indicating that post-infection care is essential for resolving these concerns. The findings underscore the need to address menstrual health and mental well-being as critical components of post-COVID treatment. Future research must concentrate on elucidating the fundamental processes of these alterations and devising targeted solutions to assist impacted people.

LIMITATIONS

Self-reported menstruation data were used in this cross-sectional investigation, which might introduce memory bias. Because the research population was limited to hospitalized patients, its applicability to the broader public is limited. Furthermore, no long-term follow-up was conducted, making it unable to evaluate how persistent the menstrual changes were.

SUGGESTIONS / RECOMMENDATIONS

Due to the substantial effects of COVID-19 on menstrual health and overall quality of life, it is advisable for healthcare personnel to meticulously observe and manage monthly abnormalities in patients after infection or immunization. Comprehensive care must include both medical therapy for menstrual disorders and psychological assistance to alleviate social and emotional repercussions. Future research must concentrate on elucidating the underlying processes of menstrual alterations after COVID, prioritizing long-term impacts and the formulation of tailored therapies. Moreover, healthcare institutions must emphasize menstrual health within post-COVID recovery strategies, guaranteeing accessible treatment and support for those impacted.

CONFLICT OF INTEREST / DISCLOSURE

The authors declare no conflict of interest related to this study.

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