SARS-CoV-2 infection and subsequent changes in the menstrual cycle among participants in the Arizona CoVHORT Study

Sana M. Khan, Alexandra Shilen, Kelly M. Heslin, Providence Ishimwe, Alicia M. Allen, Elizabeth T. Jacobs, Leslie V. Farland

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Title: SARS-CoV-2 infection and subsequent changes in the menstrual cycle among participants in the Arizona CoVHORT Study

*Sana M. Khan[1]
*Alexandra Shilen[1]
Kelly M. Heslin[1]
Providence Ishimwe[1]
Alicia M. Allen[1,2,3]
Elizabeth T. Jacobs[1,3]
Leslie V. Farland[1,3,4]

* Indicates joint contribution

[1]Department of Epidemiology and Biostatistics, Mel and Enid Zuckerman College of Public Health, University of Arizona, Tucson, AZ, United States;

[2]Department of Family and Community Medicine, University of Arizona, Tucson AZ, United States;

[3] The University of Arizona Cancer Center, Tucson, AZ, United States;

[4]Department of Obstetrics and Gynecology, College of Medicine-Tucson, University of Arizona, Tucson AZ, United States

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Corresponding Authors

Sana M. Khan, MPH
Mel and Enid Zuckerman College of Public Health, The University of Arizona
Department of Epidemiology and Biostatistics
1295 N. Martin Ave, Tucson, AZ 85724
Email: sanakhan@email.arizona.edu
phone: 928-377-9057 fax: 520-626-8009

Alexandra Shilen, MPH
Mel and Enid Zuckerman College of Public Health, The University of Arizona
Department of Epidemiology and Biostatistics
1295 N. Martin Ave, Tucson, AZ 85724
Email: alexandrashilen@arizona.edu
phone: 716-949-3743 fax: 520-626-8009

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Objective: The menstrual cycle involves complex interactions between various tissues, hormones, and organ systems. As such, the menstrual cycle is sensitive to endogenous and exogenous factors, including infection and changes in lifestyle. Over a year into the global pandemic caused by SARS-CoV-2 (COVID-19), there is increasing interest in understanding the post-acute sequalae of SARS-CoV-2 (PASC) following infection (1). Emerging evidence suggests that SARS-CoV-2 infection (2), COVID-19 vaccination, and/or psychological stress related to the COVID-19 pandemic (3) may influence the menstrual cycle. However, there is a paucity of scientific research on these topics; therefore, our objective was to describe SARS-CoV-2 infection and menstrual cycle changes.

Study Design: In May 2020, the Arizona CoVHORT Study began recruiting individuals for a prospective, population-based cohort, with the purpose of identifying the long-term consequences of COVID-19. The design of CoVHORT has been previously published (4); briefly, SARS-CoV-2 positive cases were recruited through case investigations as part of an academic-health department partnership with several health departments and testing centers across Arizona. We restricted our analysis to SARS-CoV-2 positive participants, 18-45 years old, who identified as women or non-binary and who were not currently or recently pregnant as of January 2020. Participants reporting laboratory-confirmed or suspected SARS-CoV-2 infection were administered "symptom surveys" focused on COVID-19 symptomology at approximately 6-week intervals. All study procedures were approved by the University of Arizona Institutional Review Board (#2003521636A002).

At baseline, participants reported their demographics, stress (5), and self-reported severity of COVID-19 illness (score range 0-10). Participants were also asked if they had noticed menstrual cycle changes as an ongoing or new symptom of their COVID-19 illness. If endorsed, they were asked "What changes to

your menstrual cycle have you noticed?" We compared demographics, comorbidities, self-rated COVID-19 severity, self-reported stress measured by the Perceived Stress Scale-10 (PSS-10), and COVID-19 symptomology among participants who reported a change in their menstrual cycle and those who did not. Comparisons were made using t-tests, chi-squared tests, and Poisson regression where appropriate.

Results: Of SARS-CoV-2 positive participants (n=127), 16% reported changes in their menstrual cycle (Table 1). The median number of days between a positive SARS-CoV-2 test and last reported menstrual cycle changes was 57.5 (range 28-222). Compared to SARS-CoV-2 positive participants who did not report changes, those who reported changes to their menstrual cycle were more likely to have reported a greater number of COVID-19 symptoms (8.6 vs. 6.1; p-value: 0.01) and to identify as Hispanic (50% vs. 25%; p-value: 0.03). SARS-CoV-2 positive participants who reported changes to their menstrual cycle were more likely to have an overweight/obese body mass index (60% vs. 44.9%; p-value: 0.2), and to report higher self-rated illness severity scores (5.3 vs. 2.4; p-value: 0.14) compared to those who did not report changes; however, these comparisons did not reach the threshold of statistical significance. When comparing the most-common COVID-19 symptoms, individuals who reported changes to their menstrual cycle were more likely to report fatigue (p-value: <0.01), headache (p-value: 0.002), body aches and pains (p-value: 0.002), and shortness of breath (p-value: 0.002) as COVID-19 symptoms compared to participants who did not report changes to their menstrual cycle. Among participants who reported changes to their menstrual cycle, the most common reported changes were irregular menstruation (60.0%), an increase in premenstrual syndrome symptoms (45.0%), and infrequent menstruation (35.0%).

Conclusion: The impact of COVID-19 on the menstrual cycle is largely unknown. People who reported changes in their menstrual cycle after SARS-CoV-2 infection reported more COVID-19 symptoms as compared to those who did not; however, identification of other differences between these groups were limited in this study due to the small sample size and inability to adjust for potential confounding factors. Additionally, information on COVID-19 symptoms were assessed every six weeks for SARS-CoV-2 positive participants which may lead to misclassification. The duration of menstrual cycle changes indicates the need to further investigate the role of PASC on reproductive health.

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Table 1. SARS-CoV-2 positive participants in The Arizona CoVHORT, 18-45 years old, stratified by whether they saw changes in their menstrual cycle after infection

	COVID-19 Positive Participants	
Characteristics	SARS-CoV-2 positive participants **who reported a change** in their menstrual cycle after infection[1,2] (n=20; 15.7%)	SARS-CoV-2 positive participants **who did not report a change** in their menstrual cycle after infection [1,3] (n=107; 84.3%)
Age (years), mean (sd)	30.5 (8.4)	30.6 (9.2)
Min-max	18-45	18-45
Body Mass Index (kg/m^2)[4], mean (sd)	28.1 (7.9)	27.0 (8.4)
Min-max	15.7 – 48.1	17.0 – 60.1
Body Mass Index(kg/m^2), n (%)		
< 18.5	1 (5.0)	5 (4.7)
18.5 – 24.9	7 (35.0)	54 (50.5)
25.0 – 29.9	6 (30.0)	21 (19.6)
30.0 – 39.9	4 (20.0)	17 (15.9)
>= 40	2 (10.0)	10 (9.4)
Race, n (%)		
White	14 (70.0)	96 (89.7)
Mixed Race	4 (20.0)	6 (5.6)
Prefer not to answer	2 (10.0)	2 (1.9)
Ethnicity, n (%)		
Non-Hispanic	10 (50.0)	77 (74.0)
Hispanic	10 (50.0)	26 (25.0)
Presence of a comorbid condition, n (%)	12 (60.0)	59 (55.1)
Self-rated Illness Severity Score (baseline), mean (sd)	5.3 (2.4)	4.4 (2.4)
Min-max	1-9	1-10
PSS-10 (baseline)[5], mean (sd)	22.7 (7.9)	20.7 (6.4)
Min-Max	5-32	7-35
Number of COVID-19 symptoms[6], mean (sd)	8.6 (3.5)	6.1 (4.1)
Min-Max	0-16	0-17
Changes in Menstrual Cycle, n (%)		
One or more	5 (25.0)	

missed menstrual periods		
Infrequent menstruation (i.e., menstrual periods occurring at intervals greater than 35 days)	7 (35.0)	
Irregular menstruation (i.e., the number of days your menstrual period lasts or the time between each varies significantly)	12 (60.0)	
Abnormal bleeding or spotting between normal menstrual periods	3 (15.0)	
Abnormally heavy or prolonged bleeding (i.e., bleeding for longer than a week, needing to use double the sanitary protection to control your menstrual flow)	4 (20.0)	
Abnormally light bleeding	2 (10.0)	
Increase in menstrual pain or cramps	4 (20.0)	
Increase in premenstrual syndrome symptoms (i.e., greater than usual mood swings, feelings of anxiety/depression, tiredness, trouble sleeping, bloating/stomach pain, breast tenderness, changes in appetite or sex drive)	9 (45.0)	
Most common COVID-19 symptoms, n (%)		
Fatigue	15 (79.0)	29 (27.1)
Headache	11 (57.9)	21 (19.6)
Body aches and	10 (52.6)	17 (15.9)

pains		
Shortness of breath	10 (52.6)	17 (15.9)

[1] "Have you been tested for the virus that causes CoVID19 with a nasal swab, throat swab or saliva? Or "Were you told by a medical provider that you were "presumed positive" (i.e., had COVID-19) even though you had a negative test result?".

[2]Missing values or "Prefer not to answer": self-rated severity score (n=1), PSS-10 (n=3); top reported COVID-19 symptoms (n=1)

[3]Missing values: race (n=1), ethnicity (n=4), severity score (n=18), PSS-10 baseline (n=24);

[4]BMI = body mass index;

[5]PSS-10 frames questions "In the last month have you …";

[6]COVID-19 symptoms associated with the illness described on the same survey on which the positive COVID-19 test was reported (select all that apply: fever, sore throat, cough, difficulty breathing or shortness of breath, chest pain or pressure, runny nose/cold-like symptoms, fatigue, aches and pains or muscle sores, chills, diarrhea (3 or more loose/looser than normal stools/24 hr period), nausea, vomiting, headache, loss of smell/taste, bone pain/nerve pain, conjunctivitis, rash on skin, discoloration of fingers or toes, loss of speech or movement, other)