



Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.

4. Goetsch MF, Lim JY, Caughey AB. A practical solution for dyspareunia in breast cancer survivors: a randomized controlled trial. *J Clin Oncol* 2015;33:3394–400.

5. The 2020 genitourinary syndrome of menopause position statement of the North American Menopause Society. *Menopause* 2020;27:976–92.

6. Goetsch MF. Severe postmenopausal genital pain treated successfully with prolonged estrogen therapy: a case series and narrative review. *J Low Genit Tract Dis* 2020;24:405–10.

© 2021 Elsevier Inc. All rights reserved. <https://doi.org/10.1016/j.ajog.2021.09.019>

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



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 COVID-19 pandemic caused by SARS-CoV-2, there is increasing interest in understanding the post-acute sequelae of SARS-CoV-2 (PASC) following infection.¹ Emerging evidence suggests that SARS-CoV-2 infection, COVID-19 vaccination, and/or psychological stress related to the COVID-19 pandemic may influence the menstrual cycle.^{2,3} However, there is a paucity of scientific research on these topics. Therefore, our objective was to describe SARS-CoV-2 infection and the menstrual cycle changes because of it.

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 study 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 who were 18 to 45 years old, identified as women or nonbinary, and were not currently or recently pregnant as of January 2020. The 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 the study procedures were approved by The University of Arizona Institutional Review Board (approval number 2003521636A002).

At baseline, the participants reported their demographics, stress, and the self-reported severity of COVID-19 illness (score range 0–10).⁵ The participants were also asked if they had noticed menstrual cycle changes as an ongoing symptom or a new one related to 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, and COVID-19 symptomology

among the participants who reported a change in their menstrual cycle and those who did not. The comparisons were made using *t*-tests, chi-squared tests, and Poisson regression where appropriate.

RESULTS: Among the SARS-CoV-2 positive participants ($n=127$), 16% reported changes in their menstrual cycle (Table). The median number of days between a positive SARS-CoV-2 test and the last reported menstrual cycle changes was 57.5 (range, 28–222). Compared with the SARS-CoV-2-positive participants who did not report changes, those who did report changes to their menstrual cycle were more likely to report a greater number of COVID-19 symptoms (8.6 vs 6.1; $P=.01$) and to identify as Hispanic (50% vs 25%; $P=.03$). The SARS-CoV-2-positive participants who reported changes to their menstrual cycle were more likely to be overweight or obese (60% vs 44.9%; $P=.2$) and to report higher self-rated illness severity scores (5.3 vs 4.4; $P=.14$) than 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, the individuals who reported changes to their menstrual cycle were more likely to report fatigue ($P<.01$), headache ($P=.002$), body aches and pains ($P=.002$), and shortness of breath ($P=.002$) as COVID-19 symptoms compared with the participants who did not report changes to their menstrual cycle. Among the participants who reported changes to their menstrual cycle, the most commonly 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 than those who did not. However, the identification of other differences between these groups were limited in this study owing to the small sample size and inability to adjust for potential confounding factors. In addition, information on COVID-19 symptoms was assessed every 6 weeks for SARS-CoV-2-positive participants, which may lead to misclassification. The

TABLE

SARS-CoV-2-positive participants in the Arizona CoVHORT, 18 to 45 years old and stratified by whether they saw changes in their menstrual cycle after infection

Characteristics	COVID-19 positive participants	
	SARS-CoV-2-positive participants who reported a change in their menstrual cycle after infection ^{a,b} (n = 20; 15.7%)	SARS-CoV-2-positive participants who did not report a change in their menstrual cycle after infection ^{a,c} (n = 107; 84.3%)
Age (y), mean (SD)	30.5 (8.4)	30.6 (9.2)
Age, range (y)	18–45	18–45
BMI (kg/m ²), mean (SD)	28.1 (7.9)	27.0 (8.4)
BMI, range	15.7–48.1	17.0–60.1
BMI (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 (72.0)
Hispanic	10 (50.0)	26 (24.3)
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)
Self-rated illness severity score, range	1–9	1–10
PSS-10 (baseline) ^d , mean (SD)	22.7 (7.9)	20.7 (6.4)
PSS-10, range	5–32	7–35
Number of COVID-19 symptoms ^e , mean (SD)	8.6 (3.5)	6.1 (4.1)
Number of symptoms, range	0–16	0–17
Changes in menstrual cycle, n (%)		
One or more missed menstrual periods	5 (25.0)	—
Infrequent menstruation (ie, menstrual periods occurring at intervals >35 d)	7 (35.0)	—
Irregular menstruation (ie, 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 (ie, 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)	—

Khan. SARS-CoV-2 infection and changes in the menstrual cycle in the Arizona CoVHORT study participants. *Am J Obstet Gynecol* 2022.

(continued)

TABLE

SARS-CoV-2-positive participants in the Arizona CoVHORT, 18 to 45 years old and stratified by whether they saw changes in their menstrual cycle after infection (continued)

Characteristics	COVID-19 positive participants	
	SARS-CoV-2-positive participants who reported a change in their menstrual cycle after infection ^{a,b} (n = 20; 15.7%)	SARS-CoV-2-positive participants who did not report a change in their menstrual cycle after infection ^{a,c} (n = 107; 84.3%)
Increase in premenstrual syndrome symptoms (ie, greater than usual mood swings, feelings of anxiety or depression, tiredness, trouble sleeping, bloating or 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 pains	10 (52.6)	17 (15.9)
Shortness of breath	10 (52.6)	17 (15.9)

BMI, body mass index; PSS-10, Perceived Stress Scale-10; SD, standard deviation.

^a "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' (ie, had COVID-19) even though you had a negative test result?"; ^b Missing values or "Prefer not to answer": self-rated severity score (n=1), PSS-10 (n=3); top reported COVID-19 symptoms (n=1); ^c Missing values: race (n=1), ethnicity (n=4), severity score (n=18), PSS-10 baseline (n=24); ^d PSS-10 frames questions "In the last month have you..."; ^e 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 or cold-like symptoms, fatigue, aches and pains or muscle sores, chills, diarrhea (3 or more loose/looser than normal stools per 24 hour period), nausea, vomiting, headache, loss of smell/taste, bone pain or nerve pain, conjunctivitis, rash on skin, discoloration of fingers or toes, loss of speech or movement, other).

Khan. SARS-CoV-2 infection and changes in the menstrual cycle in the Arizona CoVHORT study participants. *Am J Obstet Gynecol* 2022.

duration of menstrual cycle changes indicates the need to further investigate the role of PASC on reproductive health.

ACKNOWLEDGMENTS

We thank our Arizona CoVHORT study participants for sharing their experiences with our team. We would also like to thank Dr Kristen Pogreba-Brown, PhD, Dr Felina Cordova-Marks, DrPH, and Dr Kacey Ernst, PhD, for their involvement and leadership in designing the Arizona CoVHORT study. We thank the BIO-5 Institute at The University of Arizona for providing funding for the Arizona CoVHORT study.

Sana M. Khan, MPH
 Department of Epidemiology and Biostatistics
 Mel and Enid Zuckerman College of Public Health
 The University of Arizona
 1295 N. Martin Ave.
 Tucson, AZ 85724
sanakhan@email.arizona.edu

Alexandra Shilen, MPH
 Kelly M. Heslin, MPH
 Providence Ishimwe, BA
 Department of Epidemiology and Biostatistics
 Mel and Enid Zuckerman College of Public Health
 The University of Arizona
 Tucson, AZ

Alicia M. Allen, PhD, MPH
 Department of Epidemiology and Biostatistics

Mel and Enid Zuckerman College of Public Health
 The University of Arizona
 Tucson, AZ
 Department of Family and Community Medicine
 The University of Arizona
 Tucson, AZ
 The University of Arizona Cancer Center
 Tucson, AZ

Elizabeth T. Jacobs, PhD
 Department of Epidemiology and Biostatistics
 Mel and Enid Zuckerman College of Public Health
 The University of Arizona
 Tucson, AZ
 The University of Arizona Cancer Center
 Tucson, AZ

Leslie V. Farland, ScD
 Department of Epidemiology and Biostatistics
 Mel and Enid Zuckerman College of Public Health
 The University of Arizona
 Tucson, AZ
 The University of Arizona Cancer Center
 Tucson, AZ
 Department of Obstetrics and Gynecology
 College of Medicine-Tucson
 The University of Arizona
 Tucson, AZ

S.M.K. and A.S. have contributed equally to this work.

The authors report no conflict of interest.

The study received financial support from the BIO5 Institute at The University of Arizona (principal investigator [PI]: Kristen Pogreba-Brown and E.T.J.); and the Challenge Grant, The University of Arizona (PI: L.V.F.).

REFERENCES

1. Carfi A, Bernabei R, Landi F. Gemelli Against COVID-19 Post-Acute Care Study Group. Persistent symptoms in patients after acute COVID-19. *JAMA* 2020;324:603–5.
2. Li K, Chen G, Hou H, et al. Analysis of sex hormones and menstruation in COVID-19 women of child-bearing age. *Reprod Biomed Online* 2021;42:260–7.
3. Demir O, Sal H, Comba C. Triangle of COVID, anxiety and menstrual cycle. *J Obstet Gynaecol* 2021:1–5.
4. Catalfamo CJ, Heslin KM, Shilen A, et al. Design of the Arizona CoVHORT: a population-based COVID-19 cohort. *Front Public Health* 2021;9:620060.
5. Baik SH, Fox RS, Mills SD, et al. Reliability and validity of the perceived stress scale-10 in Hispanic Americans with English or Spanish language preference. *J Health Psychol* 2019;24:628–39.

© 2021 Elsevier Inc. All rights reserved. <https://doi.org/10.1016/j.ajog.2021.09.016>