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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 symptomatology 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=0.01) and to identify as Hispanic (50% vs 25%; P=0.03). 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=0.2) and to report higher self-rated illness severity scores (5.3 vs 4.4; P=0.14) 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<0.01), headache (P=0.002), body aches and pains (P=0.002), and shortness of breath (P=0.002) 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

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| Characteristics                                      | COVID-19 positive participants | SARS-CoV-2-positive participants who reported a change in their menstrual cycle after infection $^{ab}$ (n = 20; 15.7%) | SARS-CoV-2-positive participants who did not report a change in their menstrual cycle after infection $^{ac}$ (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/m²), mean (SD)                               | 28.1 (7.9)                     | 27.0 (8.4)                                                                                      |                                                                                                  |
| BMI, range                                           | 15.7—48.1                      | 17.0—60.1                                                                                      |                                                                                                  |
| BMI (kg/m²), 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)
duration of menstrual cycle changes indicates the need to further investigate the role of PASC on reproductive health.

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Sana M. Khan, MPH
Department of Epidemiology and Biostatistics
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

The authors report no conflict of interest.

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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 infectiona,b (n=20; 15.7%) | SARS-CoV-2-positive participants who did not report a change in their menstrual cycle after infectiona,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).

c Top reported COVID-19 symptoms (n=1).

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