


## SHORT COMMUNICATION

# Changes in RT-PCR test results and symptoms during the menstrual cycle of female individuals infected with SARS-CoV-2: Report of two cases

Hua Zheng<sup>1</sup>  | Juan Tan<sup>1</sup> | Ke Ma<sup>2</sup> | Weihua Meng<sup>3</sup>

<sup>1</sup>Department of Anesthesiology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

<sup>2</sup>Department of Infectious Disease, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

<sup>3</sup>Division of Population Health Sciences, School of Medicine, University of Dundee, Dundee, UK

## Correspondence

Juan Tan, Department of Anesthesiology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, 430030 Wuhan, China.  
Email: [msdove@126.com](mailto:msdove@126.com)

## Abstract

The implications of the menstrual cycle for disease susceptibility, development, and severity of acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection are largely unknown. Here, we describe two women infected with SARS-CoV-2 whose real-time reverse transcriptase-polymerase chain reaction (RT-PCR) test results and symptoms changed during the menstrual cycle. The first patient developed a fever on the first day of her menstrual period, and again on the first day of her next menstrual period after hospital discharge. RT-PCR test results were positive during the first menstrual period before admission, but turned negative during hospitalization, and then were positive again during the second menstrual period after hospital discharge. Another one also developed a fever again on the first day of her menstrual period after hospital discharge. RT-PCR test results were negative before admission and during hospitalization, but turned positive during the first menstrual period after hospital discharge. The cases indicate sex hormones may play an important role in SARS-CoV-2 infection. For women with history of exposure to SARS-CoV-2, the management protocol should include assessment of the menstrual status.

## KEYWORDS

COVID-19, fever, menstrual cycle, SARS-CoV-2

## 1 | BACKGROUND

The 2019 novel coronavirus infection (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has emerged as a major global health threat since December 2019.<sup>1-4</sup> As of 27 June 2020, the pandemic had registered 9 473 214 cases and 484 249 deaths worldwide.<sup>5</sup> A population level observational study by Sun et al<sup>6</sup> revealed that a sharp increase of COVID-19 was reported among people aged between 30 and 50 years, and 40% of the patients were female, indicates women of childbearing age are at high risk of infection. Growing evidence indicate that female immunity changes over the menstrual cycle.<sup>7,8</sup> However, the implications of the menstrual cycle for

disease susceptibility, development, and severity of COVID-19 are largely unknown. Here, we report the epidemiologic and clinical features of two female individuals with SARS-CoV-2 infection and the infection's association with the menstrual cycle.

## 2 | CASE PRESENTATION

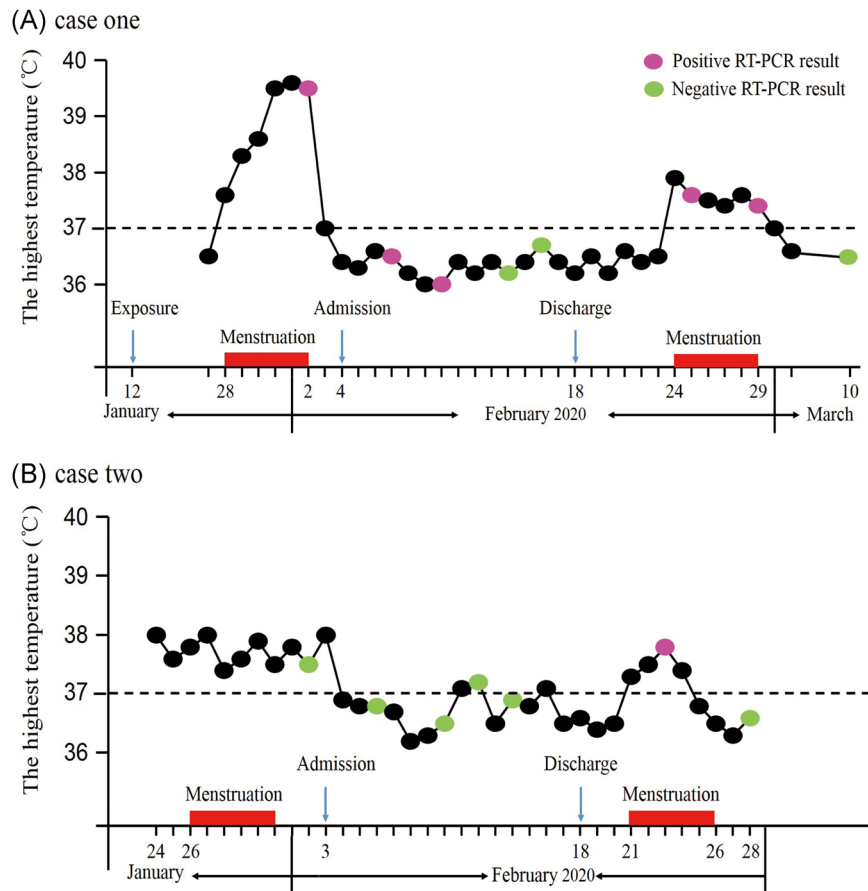
### 2.1 | Case one

A 37-year-old, previously healthy (gravida 2, para 2, regular menstrual cycle, and no history of hormonal therapies), woman had

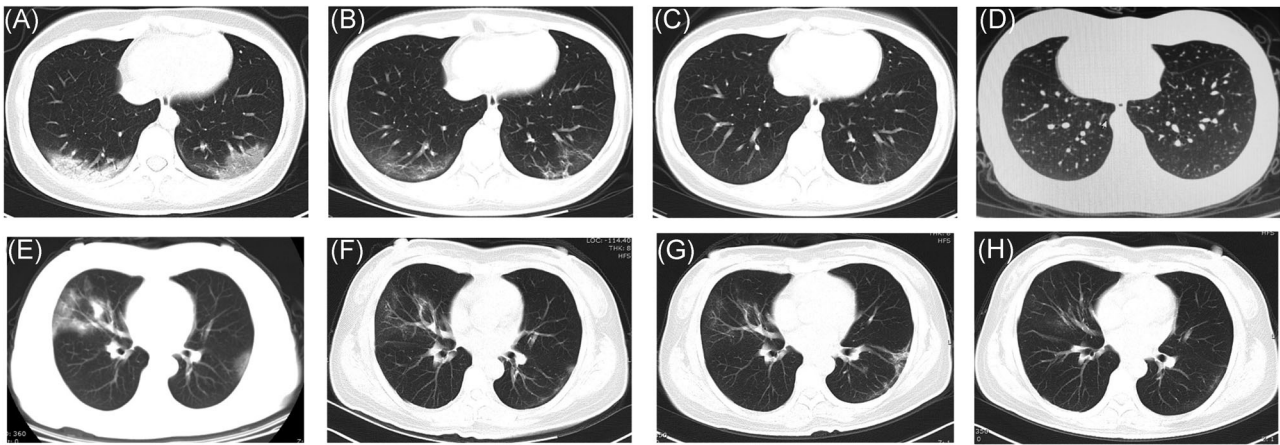
dinner with her relative on 12 January 2020. Five days later, her relative had a fever and was confirmed to be infected with SARS-CoV-2. The woman had no fever or any other gastrointestinal or respiratory symptoms until 28 January 2020, the first day of her menstrual period (Figure 1A). At first, she had only a slight and intermittent fever. However, the next day afternoon, she developed high fever, tiredness, and lack of appetite. Because of the possibility of infection with SARS-CoV-2, she was prescribed ibuprofen, oseltamivir (75 mg every 12 hours orally), arbidol (0.2g every 8 hours orally), and moxifloxacin (0.4g every day orally) by a community physician. Lopinavir and ritonavir tablets (200 mg/50 mg every 12 hours orally) were added to her antiviral regimen 2 days later. Her symptoms did not improve, which prompted her to come to the emergency department on 2 February 2020. Although chest auscultation was normal, chest computerized tomography (CT) scans showed bilateral lower lobe infiltrates (Figure 2A). Real-time reverse transcriptase-polymerase chain reaction (RT-PCR) test for nucleic

acid of SARS-CoV-2 on an oropharyngeal swab was performed as described in a previous study.<sup>2</sup> The same technician and brand of test kit (Novel Coronavirus PCR Fluorescence Diagnostic Kit, BioGerm Medical Biotechnology), which was recommended by the Chinese Center for Disease Control and Prevention, was used in this report. The result of RT-PCR test was positive. The patient was asked to self-quarantine at home because of the limited number of hospital beds in Wuhan at that time. Her temperature dropped to normal 1 day later, the last day of her menstrual period.

On 4 February 2020, the patient was hospitalized with COVID-19. On admission, the physical examination revealed body temperature of 97.5°F (36.4°C), blood pressure of 98/61mm Hg, pulse rate of 78 beats per minute, respiratory rate of 20 breaths per minute, and oxygen saturation of 95% on room air. The results of her laboratory testing showed a C-reactive protein count 12.3 mg/L (<1 mg/L indicates low risk of cardiovascular disease; 1-3 mg/L indicates medium risk of cardiovascular disease; >3mg/L indicates high risk of cardiovascular



**FIGURE 1** Timeline of changes of RT-PCR test results and symptoms during the menstrual cycle of cases infected with SARS-CoV-2. Case one (A). A, Sixteen days after exposure to SARS-CoV-2, fever occurred on the first day of her menstrual period, and again on the first day of her next menstrual period after hospital discharge. RT-PCR test results were positive during the first menstrual period before admission, turned negative during hospitalization, and then positive again during the second menstrual period, which occurred after hospital discharge. Case two (B). B, Fever occurred two days before her menstrual period, and again on the first day of her next menstrual period after hospital discharge. RT-PCR test results were negative before admission and during hospitalization, but turned positive during the first menstrual period after hospital discharge. RT-PCR indicates real-time polymerase chain reaction test for the coronavirus disease 2019 (COVID-19) nucleic acid. RT-PCR, real-time reverse transcriptase-polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2



**FIGURE 2** Transverse chest CT images of cases infected with SARS-CoV-2. Case one (A-D). Representative images of the chest CT scans showing (A) bilateral ground-glass opacity and subsegmental areas of consolidation on day 6 after symptom onset, (B) bilateral ground-glass opacity on day 12 after symptom onset, (C) bilateral patchy ground-glass opacity on day 18 after symptom onset, and (D) focal ground-glass opacity on day 29 after symptom onset. Case two (E-H). Representative images of the chest CT scans showing (E) multiple ground-glass opacity and consolidation shadow in the right upper lung lobe and left lower lung lobe on day 10 after symptom onset, (F) absorption of bilateral ground-glass opacity on day 16 after symptom onset, (G) a significant absorption of the shadow in all lesions on day 22 after symptom onset, and (H) the shadow was absorbed almost completely on day 31 after symptom onset. CT, computerized tomography; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

disease; and  $>10$  mg/L indicates infection or inflammation) and erythrocyte sedimentation rate of 30 mm/H (normal range, 10-30 mm/H). Other pertinent laboratory tests, including complete blood count, coagulation tests, liver function tests, kidney function tests, metabolic panel tests, and high-sensitivity cardiac troponin tests did not reveal any clinically significant results. A follow-up chest CT scan on 8 February 2020, showed the shadow on bilateral lung was partly absorbed (Figure 2B). Thus, all of her antiviral and antibacterial medications were canceled. RT-PCR tests for nucleic acid of SARS-CoV-2 on oropharyngeal swabs were performed 3 and 6 days after admission and the results were positive. The RT-PCR tests on oropharyngeal swabs were repeated 10 and 12 days after admission, and both showed negative results. On 14 February 2020, a repeated chest CT scan showed a further improvement of ground-glass opacification (Figure 2C). Her temperature remained normal during hospitalization. According to the criteria for hospital discharge in China including: (a) normal temperature for at least 3 days, (b) resolution of respiratory symptoms, (c) substantially improved radiological signs, and (d) negative results in two consecutive RT-PCR tests performed more than or equal to 24 hours apart, this patient was discharged on 18 February 2020.

After hospital discharge, the patient was asked to continue home quarantine for 14 days. She felt well until 24 February 2020, the first day of her menstrual period. The patient did not report contact with any other person but had fever again, peaking at 100.2°F (37.9°C). Except for tiredness, she had no other symptoms at that same time. She took arbidol (0.2 g every 8 hours orally) and moxifloxacin (0.4 g every day orally) for 3 days. The results of a RT-PCR test on 25 February 2020 and a repeated test on oropharyngeal swabs 4 days later were both positive. However, chest CT scans showed no changes from the

previous results (Figure 2D). The patient still had a slight and intermittent fever until 29 February 2020, the last day of her menstrual period. Since then, her temperature had remained normal. The RT-PCR test on oropharyngeal swab was performed on 10 March 2020, and the result was negative. However, her blood was positive for both IgG and IgM antibodies (YHLO-CLIA-IgG, YHLO-CLIA-IgM kits, YHLO Biotech Co Ltd Shenzhen, China), against SARS-CoV-2.

## 2.2 | Case two

A 44-year-old, previously healthy (gravida 1, para 1, regular menstrual cycle, and no history of hormonal therapies), woman was working as a nurse in a hospital in Wuhan, China. On 24 January, she began to have a slight fever, peaking at 100.4°F (38°C) at night (Figure 1B). Because of the possibility of infection with SARS-CoV-2 due to occupational contact history, she was prescribed arbidol (0.2 g every 8 hours orally) by a physician. On 26 January 2020, the first day of her menstrual period, she developed tiredness, muscle soreness, palpitation, and lack of appetite. She continued taking arbidol during the menstrual period, but the symptoms did not improve. On 2 February, the patient went to outpatient department in a hospital. Chest CT scans showed multiple infiltration in the bilateral lung view (Figure 2E). Blood examination showed a white blood cell count  $3.88 \times 10^9/L$  and lymphocyte count  $0.94 \times 10^9/L$ . Although the result of RT-PCR test on an oropharyngeal swab was negative, the woman was diagnosed with COVID-19 based on the occupational exposure history, symptoms and chest CT results.

On 3 February 2020, the patient was hospitalized with COVID-19. On admission, the physical examination revealed body

temperature of 99.5°F (37.5°C), blood pressure of 105/85mm Hg, pulse rate of 110 beats per minute, respiratory rate of 20 breaths per minute, and oxygen saturation of 94% on room air. The results of her laboratory testing showed a C-reactive protein count 14.8 mg/L and erythrocyte sedimentation rate of 40 mm/H. The serum-specific IgM antibodies to eight respiratory pathogens (IgM detection kit for respiratory pathogens, EUROIMMUN Co Ltd Beijing, China), including respiratory syncytial virus, adenovirus, type A and type B influenza virus, parainfluenza virus, *Legionella pneumophila*, *Mycoplasma pneumoniae*, and *Chlamydia pneumoniae*, were detected negative. Her temperature returned to normal on the next day after her admission. Thus, all of her antibacterial medications were canceled. A follow-up chest CT scan on 8 February 2020, showed decreased infiltration in both left and right lungs (Figure 2F). RT-PCR tests for nucleic acid of SARS-CoV-2 on oropharyngeal swabs were performed 3, 7, 9, and 11 days after admission and the results were negative. On 14 February 2020, a repeated chest CT scan showed a significant improvement of infiltration in all lesions (Figure 2G). Her temperature remained normal during hospitalization.

After hospital discharge on 18 February 2020, the patient was asked to continue home quarantine for 14 days. She felt well until 21 February 2020, the first day of her menstrual period. She had fever again with tiredness and dizziness, peaking at 99.3°F (37.4°C). She took arbidol (0.2 g every 8 hours orally) and moxifloxacin (0.4 g every day orally) for 5 days. The results of a RT-PCR test for nucleic acid of SARS-CoV-2 on oropharyngeal swabs on 23 February 2020 was positive. Her blood was also positive for both IgG and IgM antibodies against SARS-CoV-2 (YHLO-CLIA-IgG, YHLO-CLIA-IgM kits, YHLO Biotech Co Ltd Shenzhen, China). However, chest CT scans did not show any sign of increased infiltration (Figure 2H). The patient still had a slight and intermittent fever until 25 February 2020, the day before the last day of her menstrual period. Since then, her temperature had remained normal. The RT-PCR test on oropharyngeal swab was performed on 28 February 2020, the results were negative.

### 3 | DISCUSSION AND CONCLUSIONS

There are reported sex differences in the susceptibility and outcomes of infectious disease.<sup>9,10</sup> A recent epidemiological study of the COVID-19 outbreak shows that SARS-CoV-2 might have a longer incubation period and less pronounced symptoms in women than in men.<sup>11</sup> However, the mechanism underlying these differences remains unclear. Here, we report two women infected with SARS-CoV-2 whose RT-PCR test results and symptoms changed during the menstrual cycle. The first patient developed a fever on the first day of her menstrual period, and again on the first day of her next menstrual period after hospital discharge. RT-PCR test results were positive during the first menstrual period before admission, turned negative during hospitalization, and then positive again during the second menstrual period, which occurred after hospital discharge. Another patient also developed a fever again on the first day of her menstrual period after hospital discharge. RT-PCR test results

were negative before admission and during hospitalization, but turned positive during the first menstrual period after hospital discharge. These cases indicate sex hormones may play an important role in SARS-CoV-2 infection.

In female humans, the levels of sex hormones, largely estrogens and progesterone, vary during the menstrual cycle and decrease sharply before menstruation.<sup>12</sup> The dramatic fluctuation in sex hormone levels is associated with changes in immune function and response to respiratory virus infections.<sup>13</sup> In an animal model of influenza A virus infection, estrogen is reported to be a potent anti-inflammatory hormone and to reduce adaptive immune responses and protect hosts from influenza A virus-mediated pathogenesis.<sup>14</sup> In another animal model of the SARS-CoV infection, treatment with an estrogen receptor antagonist or ovariectomy can increase mortality in females, indicating a critical role of estrogen receptor signaling in protecting females from severe SARS-CoV infection.<sup>15</sup> Consistent with these previous studies, our findings in the current case showed a close association between symptoms, positive RT-PCR test results and the menstruation. This phenomenon might be partly explained by the findings of Chadchan et al.<sup>16</sup> They found that the expression of angiotensin converting enzyme 2 (ACE2), by which SARS-CoV-2 enters human cells, is high in human endometrial stroma and increases in the secretory phase. Furthermore, ACE2 expression in human endometrial stroma is promoted by progesterone. Future studies exploring the role and mechanism of sex hormones in the pathogenesis of SARS-CoV-2 infection are warranted.

In the first case, fever occurred on the first day and disappeared on the last day of her menstrual period. In the second case, symptoms worsened when menstruation started. These observations suggest that the menstrual status needs to be included in the observation period. During the observation period, the identification of potentially infected patients should be based on the results of RT-PCR tests or CT scans rather than symptoms.

The patients in this report had a recurrence of fever and positive RT-PCR test results during their first menstrual period after hospital discharge. Although the negative RT-PCR test results during hospitalization might be false negative,<sup>17</sup> there are increasing reports regarding positive RT-PCR test results among convalescent patients with COVID-19.<sup>18-20</sup> These observations suggest that some of the recovered patients still might be virus carriers. The management protocol for hospital discharge might need to be reevaluated, and the 14 days of home quarantine should include assessment of the menstrual status of female patients.

In summary, our report provides an initial view of the association between the menstrual cycle, symptoms and RT-PCR test results. Future studies in large cohorts are necessary to address the effect of sex hormones on the clinical course of COVID-19.

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## CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

## AUTHOR CONTRIBUTIONS

All authors discussed the results and commented on the manuscript. Specifically, HZ and JT contributed to the conception of the idea and the study design. HZ and JT prepared the data set, performed the analysis, and wrote the manuscript. KM contributed to analysis and interpretation of data. WM provided intellectual inputs for the project and critical comments on the manuscript.

## DATA AVAILABILITY STATEMENT

All data generated or analyzed during this study are included in this published article.

## ETHICS STATEMENT

Institutional Review Board (IRB) approval for this report was granted through the ethic committee of Tongji hospital, Tongji Medical College, Huazhong University of Science and Technology (TJ-C20200142). The signed consent has been obtained from the patients in this case report.

## ORCID

Hua Zheng  <http://orcid.org/0000-0003-0134-0990>

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