

# Menstrual changes after the thrombo-prophylaxis or anticoagulants used during the COVID-19 infection

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## Abstract

**Introduction:** To detect the menstrual changes after the thrombo-prophylaxis or anticoagulants used during the COVID-19 infection.

**Material and methods:** A total of 176 diagnosed with COVID-19 infection, were included in this retrospective study after giving informed consent. Participants were asked to complete an online questionnaire, and the collected participants' data were analysed using the  $\chi^2$  test to detect the menstrual changes after the thrombo-prophylaxis or anticoagulants used during the COVID-19 infection.

**Results:** The number of participants' number who reported menstrual flow for 2 to < 5 days, and menstrual flow > 7 days after the COVID-19 infection [31/176 (17.6%), and 42/176 (23.9%), respectively] was significantly higher compared to the number of participants' who reported menstrual flow for 2 to < 5 days, and menstrual flow > 7 days before the COVID-19 infection [12/176 (6.8%), and 15/176 (8.5%), respectively], ( $p = 0.005$ , and  $0.0009$ , respectively). The use of thrombo-prophylaxis or anticoagulants during the COVID-19 infection was also associated with significant menstrual pattern changes (37.8% increased menstrual flow, 18.5% menstrual flow for 2 to < 5 days, 59.7% menstrual flow > 7 days, 5.9% contact bleeding, and 6.7% abnormal menstrual pattern for one cycle).

**Conclusions:** Significant menstrual changes were observed in this study after the COVID-19 infection infection (17.6% reported menstrual flow for 2 to < 5 days, and 23.9% reported menstrual flow > 7 days). The use of thrombo-prophylaxis or anticoagulants during the COVID-19 infection infection was associated with significant menstrual changes (37.8% increased menstrual flow, 18.5% menstrual flow for 2 to < 5 days, 59.7% menstrual flow > 7 days, 5.9% contact bleeding, and 6.7% abnormal menstrual pattern for one cycle).

**Key words:** menstrual changes, thrombo-prophylaxis, anticoagulants, COVID-19 infection.

## Introduction

In 2019, several cases of pneumonia were reported in Wuhan, China. The pneumonia was later diagnosed to be caused by a novel Coronavirus Disease-19 infection (COVID-19) by the World Health Organization (WHO). In February 2020, after the spread of COVID-19 infection outside China, the COVID-19 infection outbreak was declared by the WHO [1].

Previous studies reported an abnormal coagulation (i.e. hypercoagulation status), affecting individuals infected with COVID-19 infection [2, 3]. The prevalence of venous thrombo-embolism has increased in critically ill COVID-19 infection individuals, despite prophylactic anticoagulants [4, 5]. Elevated D-dimer was reported in critically ill COVID-19 individuals; therefore, prophylactic (thromboprophylaxis) or therapeutic anticoagulants were recommended during the COVID-19 infection [6].

The causes of abnormal coagulation (i.e. hypercoagulation status) during the COVID-19 infection are

not clearly understood, but it can be explained by the endothelial injury, and immobilization of the critically ill COVID-19 infected individuals [7–9].

Endothelial injury can occur following invasion of the endothelial cells by severe acute respiratory syndrome coronavirus-2 [SARS-CoV-2 (COVID-19)] or following activation of the individual's immune inflammatory response with subsequent elevated interleukin-6 (IL-6) and markers of complement activation (i.e. C5b-9) [3, 7].

Moreover, several changes in the circulating prothrombotic factors have been reported in critically ill COVID-19 infection individuals such as elevated factor VIII and fibrinogen, circulating prothrombotic microparticles, and neutrophil extracellular traps [10].

All hospitalized COVID-19 individuals should receive thromboprophylaxis unless contraindicated according to guidelines from the American Society of Haematology, and preferably low molecular weight heparin [11].

Uterine bleeding is less common in women infected with COVID-19 infection, but it may occur, especially

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after the use of thrombo-prophylaxis or therapeutic anticoagulants [12, 13]. Abnormal uterine bleeding (AUB) is one of the common complications of anticoagulants; it causes iron deficiency anaemia, [14], and occurs in 70% of reproductive-age women receiving anticoagulants [15].

Recently a cross-sectional study found that COVID-19 infection could affect the menstrual flow pattern, and it recommended future studies to confirm this finding [16].

Therefore, the current study was designed to detect the menstrual changes after the thrombo-prophylaxis or anticoagulants used during the COVID-19 infection.

## Material and methods

A total of 176 women infected with COVID-19 infection were included in this questionnaire-based retrospective study, which was conducted from January 2021 to March 2021 at Ain Shams University, Maternity Hospital (ASMH), after approval of the study protocol by the local Institutional Review Board.

Participants were included in this questionnaire-based retrospective study, after giving their consent, following the Helsinki regulation.

COVID-19 infection was diagnosed by nasopharyngeal swab and chest CT (computerized tomography), with/without clinical findings (i.e. anosmia, dyspnoea, dry cough, and/or gastrointestinal troubles).

Inclusion criteria include reproductive-age women (> 20 and < 40 years old), who were infected with of COVID-19, regardless of whether they received thromboprophylaxis or therapeutic anticoagulants during the COVID-19 infection.

Exclusion criteria include women < 20 or > 40 years old, menopausal women, women diagnosed with AUB before the COVID-19 infection, or received thromboprophylaxis or anticoagulants within 3–6 months before this study, and refused to participate.

The PALM (defines structural AUB: polyp, adenomyosis, leiomyoma, and malignancy), and COEIN (defines functional AUB: coagulopathy, ovulatory, endometrial, iatrogenic, and non-classified) classification of AUB was used to diagnose AUB [15]. A pictorial chart was used to estimate the menstrual flow [15].

Participants were asked to complete an online questionnaire (available at: [https://docs.google.com/forms/d/e/1FAIpQLScjV2JA35\\_QdAhWqaoQsPPYfR33HX-pHVc0mv1hDIVFh9XQd2Q/viewform?vc=0&c=0&w=1&flr=0&usp=mail\\_form\\_link](https://docs.google.com/forms/d/e/1FAIpQLScjV2JA35_QdAhWqaoQsPPYfR33HX-pHVc0mv1hDIVFh9XQd2Q/viewform?vc=0&c=0&w=1&flr=0&usp=mail_form_link)), after giving informed consent.

The online questionnaire included the participants' demographic characteristics (i.e. age, marital condition, education, socio-economic level, job, and special habits); obstetric history (i.e. number of deliveries, mode of deliveries, and number of miscarriages); menstrual history (i.e. age of menarche, menstrual regularity, du-

ration of flow, number of pads used/day, associated symptoms, and average cycle length); contraceptive history (i.e. last contraceptive method used, when started, and when stopped); chronic medication history, thrombo-embolic disorders, and/or bleeding disorders; COVID-19 infection (i.e. date and method of COVID-19 diagnosis, symptoms, history of hospital, and/or intensive care unit [ICU] admission); abnormal laboratory findings; thromboprophylaxis or the anticoagulants given; and menstrual changes after COVID-19 infection (i.e. menstrual flow days, number of pads used/day, menstrual regularity, and its duration).

The collected data were analysed using the  $\chi^2$  test to detect the menstrual changes after the thromboprophylaxis or anticoagulants used during the COVID-19 infection.

## Sample size and statistical analysis

The sample size was calculated using G Power software version 3.1.9.7 [17], and  $\chi^2$  test. The qualitative variables were analysed using the  $\chi^2$  test to detect the menstrual changes after the thromboprophylaxis or anticoagulants used during the COVID-19 infection.  $P < 0.05$  was considered significant.

## Ethical considerations

Declaration of consent: The current study was conducted after approval of the study protocol by the local Institutional Review Board. Participants were included in this questionnaire-based retrospective study after giving their consent following the Helsinki regulation

## Results

A total of 176 women infected with COVID-19 were included in this questionnaire-based retrospective study to detect menstrual changes after the use of thromboprophylaxis or anticoagulants during COVID-19 infection.

The characteristics of the studied participants are listed in Table 1. Table 2 shows the studied participants' menstrual patterns and the last contraceptive methods used before COVID-19 infection.

The most common participants' symptoms during the COVID-19 infection were body aches and myalgia (21.6%), followed by fever (20.5%), and loss of taste and smell (17%).

About 26.1% (46/176) the studied women were hospitalized, 4.5% (8/176) of them were admitted to the ICU, and C-reactive protein (CRP) and lactate dehydrogenase (LDH) were the most common abnormal laboratory findings observed among the studied partici-

**Table 1.** Demographic characteristics of the studied participants

Parameters	Studied women, N = 176 (%)
<b>Marital status</b>	
Single	72 (40.9)
Married	102 (58.0)
Divorced	2 (1.1)
<b>Level of education</b>	
Intermediate school	17 (9.7)
High school	22 (12.5)
Higher education	137 (77.8)
<b>Socioeconomic status</b>	
Average	142 (80.7)
Above average	24 (13.6)
Below average	10 (5.7)
<b>Job</b>	
Medical staff	80 (45.4)
Employee	45 (25.6)
Medical student	32 (18.2)
Housewife	19 (10.8)
<b>Special habits</b>	
No	132 (75.0)
Smoking	44 (25.0)
<b>Number of deliveries</b>	
NG	74 (42.0)
Primpara	22 (12.5)
Previous 2 deliveries	36 (20.5)
Previous 3 deliveries	22 (12.5)
Previous 4 deliveries	14 (8.0)
Previous 5 deliveries	8 (4.5)
<b>Mode of delivery</b>	
No	76 (43.2)
Vaginal delivery	54 (30.7)
Cesarean section	46 (26.1)
<b>Number of miscarriages</b>	
No	130 (73.9)
One	26 (14.8)
Two	16 (9.1)
Three	2 (1.1)
Four	2 (1.1)
<b>Medical disorders</b>	
No	171 (97.2)
Bleeding disorders	2 (1.1)
Thrombotic disorders	3 (1.7)
<b>Chronic medications</b>	
No	126 (71.6)
Medications for bronchial asthma	28 (15.9)
Insulin for Diabetes	10 (5.7)
Thyroid Medications	12 (6.8)

N – number, NG – nulligravida  
Data presented as number and percentage (%).

participants [31.3% (55/176) and 30.1% (53/176), respectively] (Table 3).

Regarding the thromboprophylaxis or the anticoagulant used during the COVID-19 infection, 32.4% (57/176) of the studied participants did not receive any thromboprophylaxis and/or anticoagulants, while 43.2% (76/176) of them received thromboprophylaxis, and 24.4% (43/176) received therapeutic anticoagulant during the COVID-19 infection (Table 3).

The factor Xa inhibitor, (Xalerto®, Janssen Pharma., USA or Rivarospire®, Atico Pharm., Egypt) were used as thromboprophylaxis in 38.2% (29/76) of the studied participants during the COVID-19 infection, and acetylsalicylic acid (antiplatelet), (Aspocid®, CID Pharm., Egypt) was used as thromboprophylaxis in 30.3% (23/76) of them. Rivarospire® was used as a therapeutic anticoagulant in 41.9% (18/43) of the studied participants during the COVID-19 infection (Table 3).

### Menstrual changes during the COVID-19 infection

The number of participants who reported menstrual flow for 2 to < 5 days, and menstrual flow > 7 days after the COVID-19 infection [31/176 (17.6%) and 42/176 (23.9%), respectively] was significantly higher compared to the number of participants who reported menstrual flow for 2 to < 5 days, and menstrual flow > 7 days before the COVID-19 infection [12/176 (6.8%) and 15/176 (8.5%), respectively], ( $p = 0.005$  and  $0.0009$ , respectively) (Fig. 1, Table 4).

Moreover, the number of participants who reported normal menstrual flow days (5–7 days) after the COVID-19 infection [103/176 (58.5%)] was significantly lower compared to the number of the participants who reported normal menstrual flow days before the COVID-19 infection [149/176 (84.7%)] ( $p = 0.02$ ) (Table 4).

The number of pads used/day did not show any significant difference before or after the COVID-19 infection (Fig. 2, Table 4).

### Menstrual changes after the thrombo-prophylaxis or anticoagulants used during the COVID-19 infection

The number of participants who reported increased menstrual flow, menstrual flow for 2 to < 5 days, and menstrual flow > 7 days after the thromboprophylaxis or anticoagulants during the COVID-19 infection [45/119 (37.8%), 22/119 (18.5%), and 71/119 (59.7%), respectively] was significantly higher compared to those who did not use thromboprophylaxis or anticoagulants during the COVID-19 infection [15/57 (26.3%), 9/57 (15.8%), and 32/57 (56.1%), respectively], ( $p = 0.0002$ ,  $0.02$ , and  $0.0007$ , respectively).

**Table 2.** The studied participants' menstrual pattern and the contraceptive methods used before COVID-19 infection

Parameters	Studied women, N = 176 (%)	Parameters	Studied women, N = 176 (%)
Age of menarche		Intradermal implants	22 (12.5)
10–16	163 (92.6)	Copper intrauterine contraceptive device	34 (19.3)
> 16	13 (7.4)	Hormonal intrauterine contraceptive device	7 (4.0)
Menstrual pattern		Oral contraceptive pills	16 (9.1)
Irregular	28 (15.9)	Injectable	2 (1.1)
Regular	148 (84.1)	Natural methods	9 (5.1)
Number of menstrual flow/days		The start of the last contraception method used	
>2 < 5 days	12 (6.8)	1999	106 (60.2)
5–7 days	149 (84.7)	2009	2 (1.1)
<7 days	15 (8.5)	2011	2 (1.1)
Number of pads used/day		2012	8 (4.6)
2–5	155 (88.1)	2013	3 (1.7)
> 5	21 (11.9)	2014	3 (1.7)
Average cycle length		2015	4 (2.3)
21–35	145 (82.4)	2016	6 (3.4)
> 35	31 (17.6)	2018	8 (4.6)
Associated symptoms		2019	12 (6.8)
No symptoms	3 (1.7)	2020	12 (6.8)
Dysmenorrhea	58 (33.0)	2021	10 (5.7)
Breast tenderness	84 (47.7)	The stoppage of the last contraception method used	
Headache	5 (2.8)	Not yet stopped	148 (84.1)
Mode changes	20 (11.4)	2015	2 (1.1)
Others	6 (3.4)	2019	2 (1.1)
Last contraception method used before COVID-19 infection		2020	8 (4.6)
No	82 (46.6)	2021	16 (9.1)
Barrier method	4 (2.3)		

Data presented as number and percentage (%).

**Table 3.** Hospital and ICU admissions, abnormal laboratory findings, thromboprophylaxis, and therapeutic anticoagulant used during COVID-19 infection

Parameters	Studied women, N = 176 (%)	Parameters	Studied women, N = 176 (%)
Hospital admission		No	57 (32.4)
Yes	46 (26.1)	Thrombo-prophylaxis	76 (43.2)
No	130 (73.9)	Clexane 40 IU/24	10 (13.2)
Intensive care unit admission		Clexane 60 IU/24	7 (9.2)
Yes	8 (4.5)	Clexane 80 IU/24	3 (3.9)
No	168 (95.5)	Rivaroxaban (Rivarospire or Xalerto)	29 (38.2)
Abnormal laboratory tests during active COVID-19 infection		Acetylsalicylic acid (Aspocid)	23 (30.3)
Complete blood count	7 (4.0)	Eliquis (Apixaban)	4 (5.2)
C-reactive protein	55 (31.3)	Therapeutic anticoagulants	43 (24.4)
Lactate dehydrogenase	53 (30.1)	Clexane 40 IU/12	2 (4.6)
D-dimer	35 (19.9)	Clexane 80 IU/12	3 (7.0)
Serum ferritin	24 (13.6)	Rivarospire (Rivaroxaban)	18 (41.8)
Liver enzymes	2 (1.1)	Eliquis (Apixaban)	10 (23.3)
Anticoagulant	–	Asposid (Acetylsalicylic Acid)	10 (23.3)

Data presented as number and percentage (%).

In addition, the number of participants who reported contact bleeding, and abnormal menstrual pattern for one cycle after the thromboprophylaxis or anticoagulants during the COVID-19 infection [7/119 (5.9%) and 8/119 (6.7%), respectively] was significantly higher compared to those who did not use thromboprophylaxis or anticoagulants during the COVID-19 infection [1/57 (1.8%) and 0/57 (0%), respectively], ( $p = 0.2$  and  $0.0009$ , respectively) (Table 5).

### Discussion

A total of 176 women infected with COVID-19 were included in this questionnaire-based retrospective study, which was conducted at ASMH to detect menstrual changes after the use of thromboprophylaxis or anticoagulants during the COVID-19 infection.

External stimuli, including infections, medication, and organ dysfunctions, can easily disrupt the typical menstrual rhythm [18]. Previous studies reported menstrual abnormalities among women infected with viral infections, including hepatitis B virus (HBV), and hepatitis B virus (HCV) [19], as well as human immunodeficiency virus (HIV) [20].

#### Menstrual changes during the COVID-19 infection

The number of participants who reported menstrual flow for 2 to < 5 days, and menstrual flow > 7 days after the COVID-19 infection [31/176 (17.6%) and 42/176 (23.9%), respectively] was significantly higher compared to the number of participants who reported menstrual flow for 2 to < 5 days, and menstrual flow > 7 days before the COVID-19 infection [12/176 (6.8%) and 15/176 (8.5%), respectively], ( $p = 0.005$  and  $0.0009$ , respectively).

A retrospective cohort study including 18.076 women and examining the ovulatory and menstrual changes during the COVID-19 pandemic found that 7.7% and 19.5% of the studied participants had anovulation and abnormal menstrual cycle length, respectively, during the COVID-19 pandemic [21].

Another recent retrospective study, conducted to evaluate the menstrual changes after COVID-19 infection, found that 56.9% of the studied participants reported a change of their menstrual blood loss, and 47.2% of them reported a change of their menstrual blood loss and the number of days between 2 consecutive cycles [16].

A retrospective, cross-sectional study including 237 reproductive-age women infected with COVID-19 found that 25% of the studied women had menstrual volume changes, and 28% of them had menstrual cycle changes (mainly decreased menstrual volume or prolonged cycles) [22].

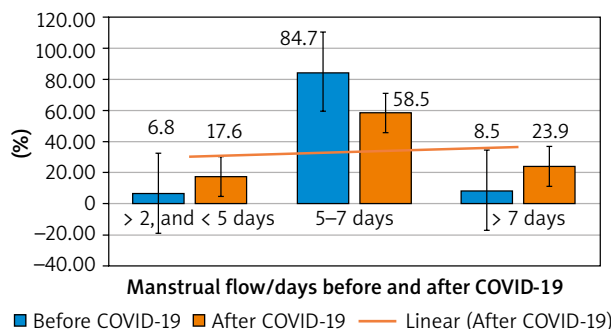


Fig. 1. Menstrual flow/days before and after COVID-19 infection

Table 4. Menstrual flow days and number of pads used/days before and after COVID-19 infection

Parameters	Before COVID-19, N = 176 (%)	After COVID-19, N = 176 (%)	p-value ( $\chi^2$ test)
Days of menstrual flow			
2 to < 5 days	12 (6.8)	31 (17.6)	0.005*
5-7 days	149 (84.7)	103 (58.5)	0.02*
> 7 days	15 (8.5)	42 (23.9)	0.0009*
Number of pads used/day			
2-5 pads/day	155 (88.1)	142 (80.7)	0.6
> 5 pads/day	21 (11.9)	34 (19.3)	0.1

\* Significant difference  
Data presented as number and percentage (%)  
 $\chi^2$  test used for statistical analysis

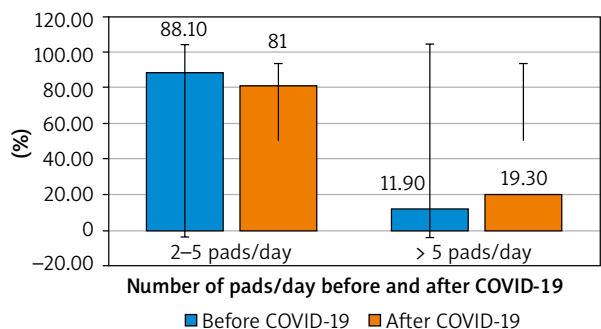


Fig. 2. Number of pads used/day before and after COVID-19 infection

The menstrual abnormalities were also reported after receiving mRNA or adenovirus vector COVID-19 vaccines, which suggest a relationship between the menstrual changes, and the host immune response rather than the virus or the vaccine components [23].

#### Menstrual changes after the thrombo-prophylaxis or anticoagulants used during the COVID-19 infection

The number of participants who reported increased menstrual flow, menstrual flow for 2 to < 5 days, and

**Table 5.** The studied participants' menstrual pattern after COVID-19 infection with or without use of thromboprophylaxis or anticoagulants

Parameters	Number of studied participants, N = 176 (%)	Without thromboprophylaxis or anticoagulants, N = 57 (%)	With thromboprophylaxis or anticoagulants, N = 119 (%)	p-value ( $\chi^2$ test)
Effect of COVID-19 infection on menstrual flow				
Increased	60 (34.1)	15 (26.3)	45 (37.8)	0.0002*
Same	77 (43.7)	29 (50.9)	48 (40.3)	0.04
Decreased	39 (22.2)	13 (22.8)	26 (21.9)	0.04
Menstrual flow days after COVID-19 infection				
2 to <5 days	31 (17.6)	9 (15.8)	22 (18.5)	0.02*
5–7 days	103 (58.5)	32 (56.1)	71 (59.7)	0.0007*
> 7 days	42 (23.9)	16 (28.1)	26 (21.8)	0.14
Number of pads used/day after COVID-19 infection				
2–5	142 (80.7)	43 (75.4)	99 (83.2)	0
> 5	34 (19.3)	14 (24.6)	20 (16.8)	0.3
Menstrual irregularities after COVID-19 infection				
No	116 (65.9)	36 (63.2)	80 (67.2)	–
Intermenstrual bleeding	27 (15.3)	12 (21.0)	15 (12.6)	0.5
Contact bleeding	8 (4.6)	1 (1.8)	7 (5.9)	0.02*
Others	25 (14.2)	8 (14.0)	17 (14.3)	0.08
Duration of abnormal menstrual pattern after COVID-19 infection				
No abnormal pattern	136 (77.3)	45 (78.9)	91 (76.5)	–
One menstrual cycle	8 (4.6)	0 (0)	8 (6.7)	0.0009*
Two menstrual cycles	24 (13.6)	9 (15.8)	15 (12.6)	0.2
Three menstrual cycles	3 (1.7)	1 (1.8)	2 (1.7)	0.5
Four menstrual cycles	4 (2.3)	2 (3.5)	2 (1.7)	1.0
Stopped after COVID-19 infection	1 (0.5)	0 (0)	1 (0.8)	0.2

\* Significant difference  
Data presented as number and percentage (%).  
 $\chi^2$  test used for statistical analysis

menstrual flow > 7 days after the thromboprophylaxis or anticoagulants during the COVID-19 infection [45/119 (37.8%), 22/119 (18.5%), and 71/119 (59.7%), respectively] was significantly higher compared to those who did not use thromboprophylaxis or anticoagulants during the COVID-19 infection [15/57 (26.3%), 9/57 (15.8%), and 32/57 (56.1%), respectively], ( $p = 0.0002, 0.02, \text{ and } 0.0007, \text{ respectively}$ ).

In addition, the number of participants who reported contact bleeding, and abnormal menstrual pattern for one cycle after the thromboprophylaxis or anticoagulants during the COVID-19 infection [7/119 (5.9%) and 8/119 (6.7%), respectively] was significantly higher compared to those who did not use thromboprophylaxis or anticoagulants during the COVID-19 infection [1/57 (1.8%) and 0/57 (0%), respectively] ( $p = 0.2 \text{ and } 0.0009, \text{ respectively}$ ).

The use of anticoagulants was listed as one of the causes of AUB in the PALM and COEIN classification of AUB [15], and it is one of the common causes

of AUB [24]. The usage of thromboprophylaxis or anticoagulants in COVID-19-infected women remains an area of debate, and there are no available guidelines regulating the use of thromboprophylaxis or anticoagulants during COVID-19 infection [25].

This study was the first questionnaire-based retrospective study conducted at ASMH, including 176 women with COVID-19 to detect the menstrual changes after the use of thromboprophylaxis or anticoagulants during the COVID-19 infection.

Significant menstrual changes were observed in this study after COVID-19 infection (17.6% of the participants reported menstrual flow for 2 to < 5 days, and 23.9% reported menstrual flow > 7 days). The use of thromboprophylaxis or anticoagulants during COVID-19 was associated with significant menstrual changes (37.8% increased menstrual flow, 18.5% menstrual flow for 2 to < 5 days, 59.7% menstrual flow > 7 days, 5.9% contact bleeding, and 6.7% abnormal menstrual pattern for one cycle). The retrospective

nature and the self-reported data were the limitations of the current study.

The menstrual changes after the COVID-19 infection and after the use of thromboprophylaxis or anticoagulants during the COVID-19 infection need to be confirmed in future studies. A guideline regulating the use of thromboprophylaxis or anticoagulants during the COVID-19 should be created and implemented.

## Conclusions

Significant menstrual changes after COVID-19 infection were observed in this study (17.6% reported menstrual flow for 2 to < 5 days, and 23.9% reported menstrual flow > 7 days). The use of thromboprophylaxis or anticoagulants during COVID-19 was associated with significant menstrual changes (37.8% increased menstrual flow, 18.5% menstrual flow for 2 to < 5 days, 59.7% menstrual flow > 7 days, 5.9% contact bleeding, and 6.7% abnormal menstrual pattern for one cycle).

## Disclosure

The authors report no conflict of interest.

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