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# Different pattern of menstrual in patients with COVID-19 infections

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## Abstract

**Objective:** To investigate the impact of COVID-19 infection on menstrual pattern with or without use of anticoagulation therapy.

**Methods:** A retrospective study was conducted on 175 female patients, diagnosed with COVID-19 to assess the pattern of menstrual changes after infection using an online based questionnaire.

**Results:** There is highly significant results between number of menstruation days before and after COVID infection with P value ($p<0.001$) among the studied patients without use of anticoagulation. No statistically significant difference between without anti-coagulation and with anti-coagulation according to the effect of COVID-19 infection on menstrual flow, the number of menstrual flow days' post COVID-19 infection, the number of pads per day post-COVID-19 infection, post-COVID-19 menstrual irregularity, if there is abnormal menstrual pattern after COVID-19 infection and action after abnormal menstrual pattern, with p-value ($p>0.05$ NS).

**Conclusion:** COVID-19 infection has a direct effect of menstrual pattern regarding the duration of menstruation in infected females irrespective of the use of anticoagulants in the treatment plane. However, it hasn't direct effect on regularity or amount of menstrual flow.

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## Introduction

A novel coronavirus was identified in late 2019 that rapidly reached pandemic proportions. The World Health Organization has designated the disease caused by the virus (severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]) as coronavirus disease 2019 (COVID-19).[1]

Many reports have described Individuals with COVID-19 may suffer from coagulation abnormalities (a

hypercoagulable state associated with COVID-19).[2][3] The prevalence of venous thromboembolism (VTE) is increased, especially in critically ill individuals, despite prophylactic anticoagulation.[4] Arterial thrombosis has also been reported but the prevalence is not known.[5] Elevated D-dimer has a direct relation with a worse prognosis. So different approaches were described how to use prophylactic and therapeutic anticoagulation in patients with COVID-19.[6]

The pathogenesis of hypercoagulability in COVID-19 is incompletely understood. Virchow's triad, (hypercoagulability can be thought of in terms of Virchow's triad). All three of the major contributions to clot formation apply to severe COVID-19 infection: Endothelial injury, through direct invasion of endothelial cells by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viruses. Other sources of endothelial injury include host immune response, intravascular catheters, the mediators of the acute systemic inflammatory response like interleukin [IL]-6 and other acute phase reactants and the contribution of complement-mediated endothelial injury may have a role. Increased markers of complement activation such as C5b-9 in the circulation of individuals hospitalized with COVID-19 than in controls (healthy people, people in the intensive care unit with non-COVID-19 respiratory failure, or people with influenza).[3][7]

Immobilization can cause stasis of blood flow in all hospitalized and critically ill patients, regardless of whether they have COVID-19 infection.[8][9]

Hypercoagulable state, a number of changes in circulating prothrombotic factors have been reported or proposed in patients with severe COVID-19. Elevated factor VIII, Elevated fibrinogen, and Circulating prothrombotic microparticles and neutrophil extracellular traps (NETs).[10]

All hospitalized medical, surgical, and obstetric patients with COVID-19 should receive thromboprophylaxis unless contraindicated according to guidelines from the American Society of Hematology (ASH). Low molecular weight (LMW) heparin is preferred, but unfractionated heparin can be used if LMW heparin is unavailable or if there is an impairment in kidney functions. Other protocols include more aggressive anticoagulation with intermediate-dose or even therapeutic-dose anticoagulation for thromboprophylaxis.[11]

Bleeding is less common than clotting in patients with COVID-19,[12] but it may occur, especially in the setting of anticoagulation. Bleeding is likely multifactorial, related to the COVID-19 illness severity or anticoagulation. If it occurs, treatment is similar to non-COVID-19 patients and may include transfusions, anticoagulant reversal or discontinuation, or specific products for underlying bleeding disorders.[13]

But here will concentrate on Heavy menstrual bleeding (HMB) which is one of the most common complications of anticoagulation use, it represents about 70% of menstruating women receiving oral anticoagulation but actually, it is lesser with new generations of oral anticoagulation like apixiban. HMB can result in iron deficiency anemia, decrease quality of life.[14] So, we will investigate the effect of anticoagulation use on menstrual flow on patient who had COVID- 19 infection or it is one of the effects of the viral infection itself.

## Patients and Methods

Aquestionnaire based retrospective study was conducted on 175 ladies, diagnosed with COVID-19, at Maternity Hospital (inpatient, ER, and outpatient clinic), Ain Shams University, during the period from January 2021 to March 2021. All 175 patients were diagnosed either by nasopharyngeal swab, CT chest or based upon suspected clinical findings e.g.;

anosmia, dyspnea, dry cough, GIT troubles. Inclusion criteria include female patients in child bearing period with past history of COVID-19 infection, menopausal patients were excluded.

Online based questionnaire was implemented (Available at: https://docs.google.com/forms/d/e/1FAIpQLScjV2JA35_QdAhWqaoQsPPyfR33HXpHVc0mv1hDlVFh9XQd2Q/viewform?vc=0&c=0&w=1&flr=0&usp=mail_form_link), including patient demographic data (age, marital status, level of education, socioeconomic status, job and special habits of consideration), obstetric history (number of deliveries, mode of deliveries and number of abortions), menstrual history (age of menarche, menstrual flow regularity, duration of flow, number of pads used/day, passage of blood clots, associated symptoms and average cycle length), contraceptive history (last method used, when started and when stopped), past history of (medications received, thromboembolic disorders, bleeding disorders or abnormal uterine bleeding), COVID-19 infection (date of diagnosis, method of diagnosis, symptoms, history of hospital or ICU admission, laboratory tests abnormality and treatment that was given including type, dose and duration of anticoagulation), menstrual changes post COVID-19 infection (menstrual regularity, menstrual flow days, number of pads used/day, average cycle length, if there was change in menstrual pattern for how long and how managed).

**Statistical analysis:** Recorded data were analyzed using the statistical package for social sciences, version 23.0 (SPSS Inc., Chicago, Illinois, USA). The quantitative data were presented as mean± standard deviation and ranges. Also, qualitative variables were presented as number and percentages. ***The following tests were done:*** Chi-square ($x^2$) test of significance was used in order to compare proportions between qualitative parameters. The confidence interval was set to 95% and the margin of error accepted was set to 5%. So, the p-value was considered significant as the following: Probability P-value <0.05 was considered significant.

## Results

Table 1 demonstrates demographic data and personal history of all patients are demonstrated in. Detailed data about the menstrual pattern and the used contraceptive methods before COVID-19 infection are illustrated in Table 2.

As regards anticoagulant use among the infected patients, 57 patients (32.4%) did not receive anticoagulants, 76 patients (43.2%) received prophylactic anticoagulation mainly asposid (30.3%), and 43 patients (24.4%) received therapeutic anticoagulation mainly revaspire (41.9%) (Table 6).

After COVID-19 infection, changes in menstruation are summarized in Table 5. Our results showed a statistically highly significant difference between the pattern of menstruation before COVID infection and menstruation after COVID infection according to the number of days of menstruation, with a p-value ($p<0.001$) (Table 6) (Figures 1 & 2), with no effects on menstrual flow, number of used bad or menstrual irregularity.

Table 7 shows no statistically significant difference between without anti-coagulation and with anti-coagulation according to Effect of COVID-19 infection on menstrual flow, Number of menstrual flow days' post COVID-19 infection, Number of pads per day post-COVID-19 infection, Post COVID-19 menstrual irregularity, if there is abnormal menstrual pattern after COVID-19 infection and Action after abnormal menstrual pattern, with p-value ($p>0.05$ NS).

## Discussion

Various external stimuli, including infections, medication, and organ dysfunctions can easily disrupt the typical menstruation rhythm.[15] In previous studies, menstrual abnormalities were demonstrated among females infected with viral infections, including hepatitis B virus (HBV) and hepatitis B virus (HCV)[16] as well as human immunodeficiency virus (HIV).[17]

Based on online-based questionnaire, we tried to explore the effect of COVID infection on menstruation. We reported that the number of menstruation days before and after COVID infection were significantly different ($p<0.001$) among our patients, indicating obvious effects of viral infection on the menstrual cycle. By analyzing the menstrual changes of COVID-19 patients, it was found that the menstruation of more than half of patients remains from 2-7 days after infection, however, in some patients, the days of menstruation increased more than before infection and in other patients, it decreased or even stopped.

In the same context, in a retrospective study by Nguyen et al.[18] who examined changes in ovulation and menstruation among 18,076 women from more than 60 developing countries using the Natural Cycles mobile tracking app. They demonstrated a statistically significant decrease in cycle length and increase in the menses duration at the population level.

Also, Li et al.[19] study on menstruating females showed that about one-fifth of those infected with COVID-19 experienced a menstrual disturbance in the form of cycle prolongation and decrease menstrual volume. They attributed these disturbances to temporary changes in sex hormones resulting from transient ovarian suppression that resolved after a short period.

On the other hand, menstrual abnormalities have been described after receiving mRNA and adenovirus vectored COVID-19 vaccines, attributing these changes to immunological response to the vaccine rather than a certain vaccine component.[20]

The usage of anticoagulants in COVID-19 remains an area of debate with no definite guidelines published to date highlighting the drug of choice, the timing, dosage, and duration of anticoagulation.[13][21] Anticoagulant-associated heavy menstrual bleeding is one of the frequent side effects of anticoagulant use.[14][22]

To investigate the effect of anticoagulant use on menstruation, we asked the patients about their menstrual flow, menstrual irregularities, number of menstrual flow days, number of used pads per day, abnormal menstrual pattern, and action after abnormal menstrual pattern before and after anticoagulant, and we found no statistically significant differences before and after the use anticoagulant in terms of menstrual changes ($p>0.05$). These results revealed no effect of anticoagulant use on menstruation in COVID patients yet these findings could be explained by the non-prolonged use of anticoagulants which actually is stopped shortly after treating the infection.

In summary, we concluded that the use of anticoagulants in COVID patients has a negligible effect on the menstrual rhythm. We assumed that the potential trigger for menstrual abnormalities could be due to increased stress caused by the pandemic and fear of deterioration of the disease and worries about the consciousness since the majority of our patients were married and had children. In an animal study, it was found that psychological stress leads to an increase in cortisol level and superoxide dismutase (SOD) activity causing anovulation and menstrual abnormalities in stressed mice.[15]

Being retrospective and self-reported work, these were the main limitations of our study. In addition, we did not take

into consideration other variables that could affect the typical menstrual pattern such as an increase in body mass index (BMI), other inherited bleeding disorders, etc. Finally, this study was performed in only one hospital with limited sample size.

## Conclusion

COVID-19 infection may be a direct cause of menstrual changes in infected females irrespective of the use of anticoagulants in the treatment protocol as we reported no significant difference on menstruation after receiving anticoagulants in COVID-19 patients.

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**Author contributions:** Protocol design: Professor Alaa El-feky; Data collection, analysis: Rania G. El-Skaan, Omnia B. Bakr; Manuscript writing: Rania G. El-Skaan, Omnia B. Bakr.

**Data availability statement**: Data can be shared if required.

## Tables

***Table (1):*** *Demographic data distribution among study group (n=176).*

| Demographic data (n=176) | No. | % |
|---|---|---|
| **Marital status** | | |
| Single | 72 | 40.9% |
| Married | 102 | 58.0% |
| Divorced | 2 | 1.1% |
| **Level of education** | | |
| Intermediate school | 17 | 9.7% |
| High school | 22 | 12.5% |
| Higher education | 137 | 77.8% |
| **Socioeconomic status** | | |
| Average | 142 | 80.7% |
| Above average | 24 | 13.6% |
| Below average | 10 | 5.7% |
| **Job** | | |
| Medical staff | 80 | 45.5% |
| Employee | 45 | 25.6% |
| Medical student | 32 | 18.2% |
| House wife | 19 | 10.8% |

| | | |
|---|---|---|
| **Special habits and considerations** | | |
| No | 132 | 75.0% |
| Smoking | 44 | 25.0% |
| **Number of deliveries** | | |
| NG | 74 | 42.0% |
| P1 | 22 | 12.5% |
| P2 | 36 | 20.5% |
| P3 | 22 | 12.5% |
| P4 | 14 | 8.0% |
| P5 | 8 | 4.5% |
| **Mode of delivery** | | |
| No | 76 | 43.2% |
| Vaginal delivery | 54 | 30.7% |
| Cesarean section | 46 | 26.1% |
| **Number of abortions** | | |
| No | 130 | 73.9% |
| One | 26 | 14.8% |
| Two | 16 | 9.1% |
| Three | 2 | 1.1% |
| Four | 2 | 1.1% |
| **Medical disorders** | | |
| No | 144 | 81.8% |
| Abnormal uterine bleeding | 27 | 15.3% |
| Bleeding disorders | 2 | 1.1% |
| Thrombotic disorders | 3 | 1.7% |
| **Chronic medications use** | | |
| No | 42 | 23.9% |
| BA | 28 | 15.9% |
| Insulin | 10 | 5.7% |
| Ant thyroid | 12 | 6.8% |

***Table (2):*** *Pattern of menstruation Before COVID infection distribution among study group*

| **Pattern of menstruation Before COVID infection (n=176).** | **No.** | **%** |
|---|---|---|
| **Age of menarche** | | |
| 10-16 | 163 | 92.6% |
| >16 | 13 | 7.4% |
| **Menstrual regularity** | | |
| Irregular | 28 | 15.9% |

| | | |
|---|---|---|
| Regular | 148 | 84.1% |
| **Number of days** | | |
| <2 days | 12 | 6.8% |
| 2-7 days | 149 | 84.7% |
| <7 days | 15 | 8.5% |
| **Number of pads per day** | | |
| 2-5 | 155 | 88.1% |
| >5 | 21 | 11.9% |
| **Passage of blood clots** | | |
| No | 57 | 32.4% |
| Yes | 119 | 67.6% |
| **Average cycle length** | | |
| 21-35 | 145 | 82.4% |
| >35 | 31 | 17.6% |
| **Associated symptoms** | | |
| No symptoms | 3 | 1.7% |
| Dysmenorrhea | 58 | 33.0% |
| Breast tenderness | 84 | 47.7% |
| Headache | 5 | 2.8% |
| Mode changes | 20 | 11.4% |
| Others | 6 | 3.4% |
| **Last contraception method** | | |
| No | 82 | 46.6% |
| Barrier method | 4 | 2.3% |
| Intradermal capsule | 22 | 12.5% |
| Cupper IUCD | 34 | 19.3% |
| Hormonal IUCD | 7 | 4.0% |
| Oral contraceptive pills | 16 | 9.1% |
| Injectable | 2 | 1.1% |
| Natural methods | 9 | 5.1% |
| **Start of use of last contraception method** | | |
| 1999 | 106 | 60.2% |
| 2009 | 2 | 1.1% |
| 2011 | 2 | 1.1% |
| 2012 | 8 | 4.5% |
| 2013 | 3 | 1.7% |
| 2014 | 3 | 1.7% |
| 2015 | 4 | 2.3% |
| 2016 | 6 | 3.4% |
| 2018 | 8 | 4.5% |
| 2019 | 12 | 6.8% |

| | | |
|---|---|---|
| 202 | 12 | 6.8% |
| 2021 | 10 | 5.7% |
| **Stoppage of last contraception method** | | |
| Not Yet | 148 | 84.1% |
| 2015 | 2 | 1.1% |
| 2019 | 2 | 1.1% |
| 202 | 8 | 4.5% |
| 2021 | 16 | 9.1% |

***Table (3):*** *Hospital admission, ICU admission and Abnormal laboratory tests during active COVID-19 infection distribution among study group (n=176).*

| | | |
|---|---|---|
| **Hospital admission** | | |
| Yes | 46 | 26.1% |
| No | 130 | 73.9% |
| **ICU admission** | | |
| Yes | 8 | 4.5% |
| No | 168 | 95.5% |
| **Abnormal laboratory tests during active COVID-19 infection** | | |
| CBC | 7 | 4.0% |
| CRP | 55 | 31.3% |
| LDH | 53 | 30.1% |
| D-Dimer | 35 | 19.9% |
| Serum ferritin | 24 | 13.6% |
| Liver enzymes | 2 | 1.1% |

***Table (4):*** *Anticoagulation use distribution among study group (n=176).*

| Anticoagulation use | No. | % |
|---|---|---|
| ***Don't received Anticoagulation** | **57** | **32.4%** |
| ***Prophylactic Anticoagulation** | **76** | **43.2%** |
| *-Clexane 40 IU/24* | *10* | *13.2%* |
| *-Clexane 60 IU/24* | *7* | *9.2%* |
| *-Clexane 80 IU/24* | *3* | *3.9%* |
| *-Asposid* | *23* | *30.3%* |
| *-Revaspire* | *22* | *28.9%* |
| *-Eliquis* | *4* | *5.3%* |
| *-Xalerto* | *7* | *9.2%* |
| ***Therapeutic** | **43** | **24.4%** |
| *-Clexane 40 IU/12* | *2* | *4.7%* |
| *-Clexane 80 IU/12* | *3* | *7.0%* |
| *-Revaspire* | *18* | *41.9%* |
| *-Eliquis* | *10* | *23.3%* |
| *-Asposid* | *10* | *23.3%* |

***Table (5):*** *Menstruation after COVID infection distribution among study group (n=176).*

| Menstruation After COVID infection | No. | % |
|---|---|---|
| **Effect of COVID-19 infection on menstrual flow** | | |
| Increased | 60 | 34.1% |
| Same | 77 | 43.8% |
| Decreased | 39 | 22.2% |
| **Number of menstrual flow days post COVID-19 infection** | | |
| <2 days | 31 | 17.6% |
| 2-7 days | 103 | 58.5% |
| >7 days | 38 | 21.6% |
| Stopped | 4 | 2.3% |
| **Number of pads per day post COVID-19 infection** | | |
| 2-5 | 142 | 80.7% |
| >5 | 34 | 19.3% |
| **Post COVID-19 menstrual irregularity** | | |
| No | 116 | 65.9% |
| Intermenstrual bleeding | 27 | 15.3% |
| Contact bleeding | 8 | 4.5% |
| Others | 25 | 14.2% |
| **If there is abnormal menstrual pattern after COVID-19 infection, for how many cycles** | | |
| No | 136 | 77.3% |
| One | 8 | 4.5% |
| Two | 24 | 13.6% |
| Three | 3 | 1.7% |
| Four | 4 | 2.3% |
| Stopped after infection | 1 | 0.6% |
| **Action after abnormal menstrual pattern** | | |
| No thing | 152 | 86.4% |
| Stop anticoagulation | 18 | 10.2% |
| Add drugs to stop medications | 2 | 1.1% |
| Add hormonal treatment | 4 | 2.3% |

***Table (6):*** *Comparison between Pattern of menstruation Before COVID infection and Menstruation after COVID infection according to Number of days of menstruation and Number of pads per day.*

| Menstruation | Pattern of menstruation Before COVID infection | | Menstruation After COVID infection | | Chi-square test | |
|---|---|---|---|---|---|---|
| | No. | % | No. | % | x2 | p-value |
| **Number of days of menstruation** | | | | | | |
| <2 days | 12 | 6.8% | 31 | 17.6% | 30.773 | <0.001** |
| 2-7 days | 149 | 84.7% | 103 | 58.5% | | |
| >7 days | 15 | 8.5% | 38 | 21.6% | | |
| Stopped | 0 | 0.0% | 4 | 2.3% | | |
| **Number of pads per day** | | | | | | |
| 2-5 pads/day | 155 | 88.1% | 142 | 80.7% | 3.103 | 0.078 |
| >5 pads/day | 21 | 11.9% | 34 | 19.3% | | |

*Using: Chi-square test*

*p-value >0.05 NS; **p-value <0.001 HS*

***Table (7):*** *Comparison between Without Anti-coagulation and with Anti-coagulation according to Menstruation after COVID infection.*

| Menstruation After COVID infection | Without Anti-coagulation | | With Anti-coagulation | | Chi-square test | |
|---|---|---|---|---|---|---|
| | No. | % | No. | % | x2 | p-value |
| **Effect of COVID-19 infection on menstrual flow** | | | | | | |
| Increased | 15 | 26.3% | 45 | 37.8% | 2.490 | 0.288 |
| Same | 29 | 50.9% | 48 | 40.3% | | |
| Decreased | 13 | 22.8% | 26 | 21.8% | | |
| **Number of menstrual flow days post COVID-19 infection** | | | | | | |
| <2 days | 9 | 15.8% | 22 | 18.5% | 1.152 | 0.765 |
| 2-7 days | 32 | 56.1% | 71 | 59.7% | | |
| >7 days | 14 | 24.6% | 24 | 20.2% | | |
| Stopped | 2 | 3.5% | 2 | 1.7% | | |
| **Number of pads per day post COVID-19 infection** | | | | | | |
| 2-5 pads/day | 43 | 75.4% | 99 | 83.2% | 1.487 | 0.223 |
| >5 pads/day | 14 | 24.6% | 20 | 16.8% | | |
| **Post COVID-19 menstrual irregularity** | | | | | | |
| No | 36 | 63.2% | 80 | 67.2% | 3.336 | 0.343 |
| Intermenstrual bleeding | 12 | 21.1% | 15 | 12.6% | | |
| Contact bleeding | 1 | 1.8% | 7 | 5.9% | | |
| Others | 8 | 14.0% | 17 | 14.3% | | |
| **If there is abnormal menstrual pattern after COVID-19 infection** | | | | | | |
| No | 45 | 78.9% | 91 | 76.5% | 5.196 | 0.392 |
| One | 0 | 0.0% | 8 | 6.7% | | |
| Two | 9 | 15.8% | 15 | 12.6% | | |
| Three | 1 | 1.8% | 2 | 1.7% | | |
| Four | 2 | 3.5% | 2 | 1.7% | | |
| Stopped after infection | 0 | 0.0% | 1 | 0.8% | | |
| **Action after abnormal menstrual pattern** | | | | | | |
| No thing | 52 | 91.2% | 100 | 84.0% | 4.802 | 0.187 |
| Stop anticoagulation | 2 | 3.5% | 16 | 13.4% | | |
| Add drugs to stop medications | 1 | 1.8% | 1 | 0.8% | | |
| Add hormonal treatment | 2 | 3.5% | 2 | 1.7% | | |

*Using: Chi-square test; p-value >0.05 NS*

## Figures

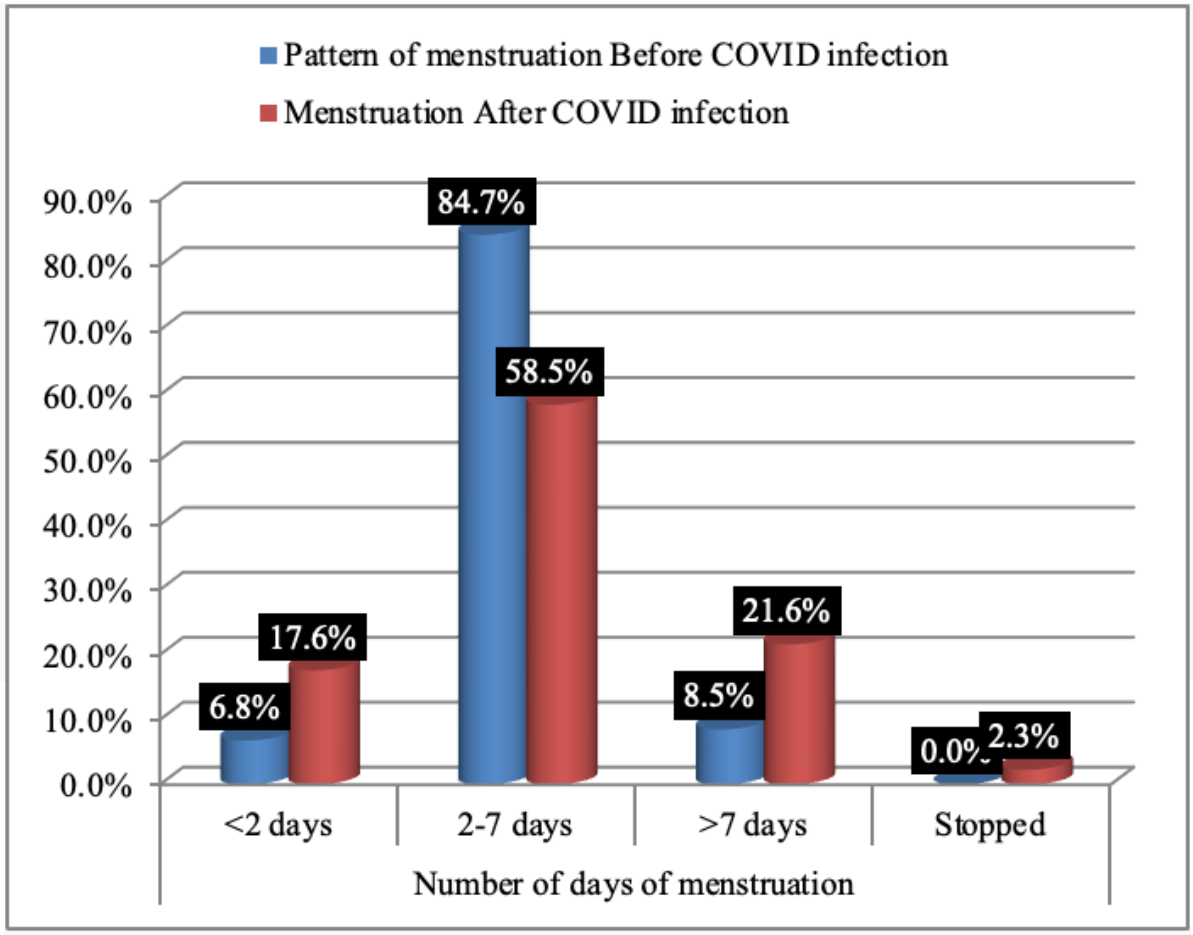


***Figure 1.*** *Comparison between Pattern of menstruation Before COVID infection and Menstruation after COVID infection according to Number of days of menstruation.*

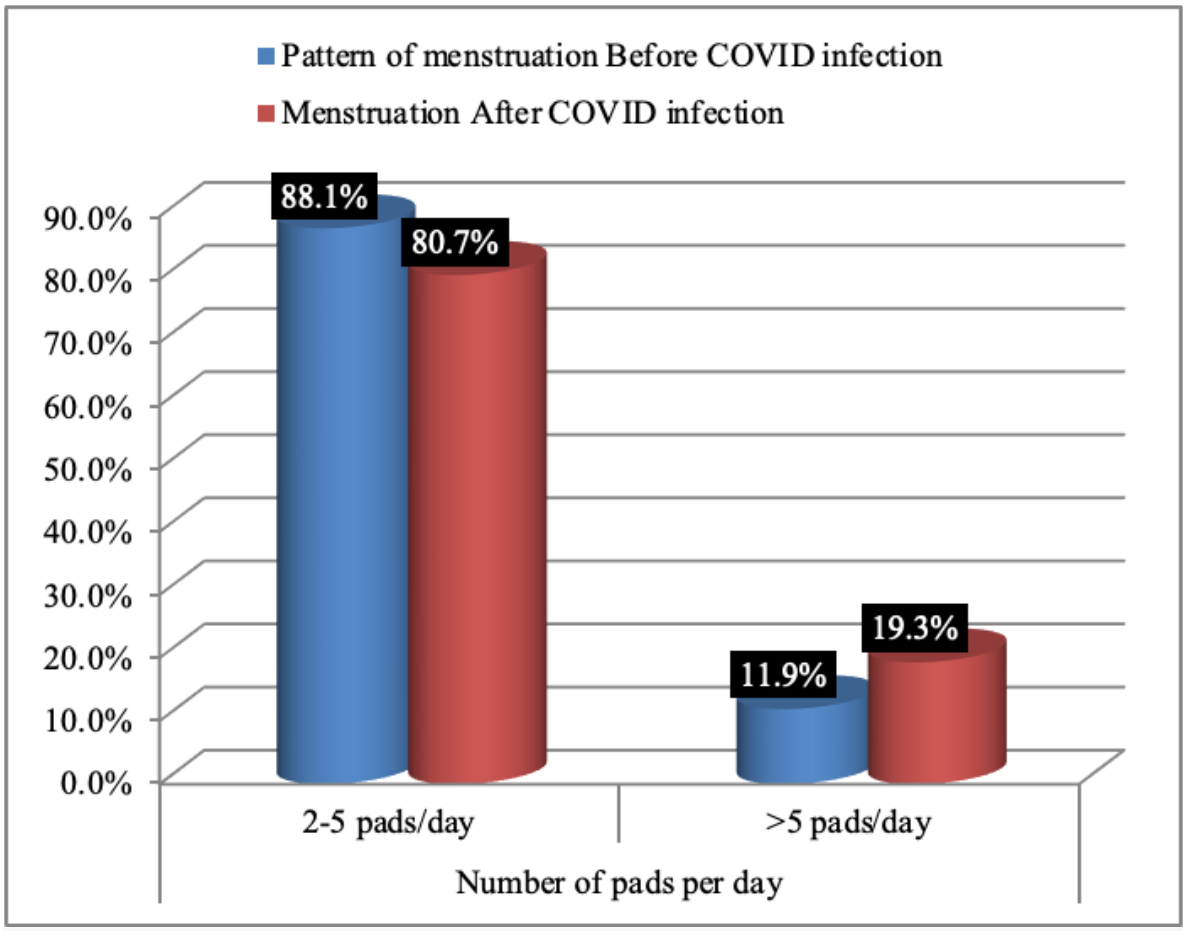


***Figure 2.*** *Comparison between Pattern of menstruation Before COVID infection and Menstruation after COVID infection according to Number of pads per day.*

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