

# The Effects of the COVID - 19 Pandemic on Abnormal Uterine Bleeding According to the PALM-COEIN Classification

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## ABSTRACT

**OBJECTIVE:** To investigate the impact of the COVID - 19 pandemic on abnormal uterine bleeding (AUB) according to the PALM-COEIN classification.

**STUDY DESIGN:** Patients who underwent surgical intervention due to AUB were categorized according to the PALM-COEIN classification, and the pandemic period was compared with the pre-pandemic period.

**RESULTS:** During the COVID - 19 pandemic, an increase in abnormal uterine bleeding (AUB) was observed. This was statistically shown to be due to ovulatory dysfunction and endometrial problems (with p-values of 0.033 and 0.024, respectively). No significant changes were detected in categories including polyp, adenomyosis, leiomyoma, malignancy, and iatrogenic causes ( $p > 0.05$ ).

**CONCLUSIONS:** In the relationship between COVID - 19, ovulatory dysfunction, and endometrial issues, several factors should be considered. These include direct inflammation of the ovarian and endometrial tissues, potential defects in endometrial repair mechanisms secondary to inflammation, changes in the hypothalamic-pituitary-ovarian axis, immunological effects of vaccination, systemic inflammatory responses affecting the ovary and endometrium, changes in inflammatory and immune mediators, and immune cell activation. Additionally, increased production of vasodilatory substances such as prostaglandin E2 and prostacyclin, decreased production of local vasoconstrictors like prostaglandin F2 $\alpha$  and endothelin-1, as well as increased plasminogen activator activity leading to enhanced thrombolysis and disruptions in endometrial hemostatic mechanisms.

**Keywords:** Abnormal uterine bleeding, COVID - 19 pandemic, PALM-COEIN classification

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## Introduction

Abnormal uterine bleeding (AUB) is defined by the International Federation of Gynecology and Obstetrics (FIGO) as abnormal bleeding unrelated to pregnancy in terms of duration, frequency, or amount, originating from the uterine corpus. Its prevalence varies among populations but remains the most common gynecological event, affecting approximately 30% of cases (1). AUB has a detrimental impact on patients' quality of life and carries significant physical, social, and emotional consequences (2). The lack of consensus, confusion, and the absence of standardized classification methods in AUB categorization have hindered its diagnosis, treatment, and clinical research for a considerable period. To address this issue, FIGO designed the comprehensive PALM - COEIN classification to standardize the diagnosis, pathogenesis, and management of AUB (3). The PALM - COEIN acronym is now widely used to categorize the causes of AUB: polyp (AUB - P), adenomyosis (AUB - A), leiomyoma (AUB -

L), malignancy and hyperplasia (AUB - M), coagulopathy (AUB - C), ovulatory dysfunction (AUB - O), endometrial (AUB - E), iatrogenic (AUB - I), and not otherwise classified (AUB - N). "PALM" categorizes structural problems, while "COEIN" classifies functional issues.

The COVID - 19 pandemic has had significant health, economic, and social consequences for many individuals (4). Research indicates that SARS - CoV - 2 infection or COVID - 19 vaccination may lead to changes in menstrual cycles (5,6). However, the effects of the COVID - 19 pandemic on menstruation have not yet been systematically investigated.

Menstruation is regulated by the hypothalamic-pituitary-ovary axis and reflects the overall health of reproductive-age women. Menstrual regularity can be sensitive to a wide range of factors, including stress, weight changes, diet, and medication use (7). Moreover, acute viral infections have been shown to contribute to menstrual disturbances (e.g., dysmenorrhea or oligomenorrhea, menorrhagia) through pathways such as immune system alterations and direct inflammation of the ovaries (8,9). Studies have reported an increase in changes in menstrual characteristics during the COVID - 19 pandemic, but the findings are inconsistent (10,11).

Since the spread of COVID - 19 in March 2020, there have been fluctuations in case numbers worldwide, with various countries experiencing peaks and valleys, and some even facing second or third waves (12). In our study, we retrospectively examined the prevalence of abnormal uterine bleeding and changes in menstrual characteristics among reproductive-age women during the COVID - 19 pandemic period.

## Material and Method

Medical records of reproductive-age patients (18-55 years old) who underwent hysteroscopy, endometrial biopsy, therapeutic curettage, myomectomy, or hysterectomy for abnormal uterine bleeding (AUB) with pathology evaluation were retrospectively reviewed between March 1, 2018, and April 1, 2022, using the hospital's record system. Data on patients' age, height, weight, gravidity, parity, blood type, hepatitis markers, physical examination findings, abdominal or vaginal ultrasound findings, and any imaging test results (such as MRI or CT), as well as pathology results, were examined. Factors related to pregnancy or pregnancy-associated factors, cervical smear abnormalities, bleeding associated with the cervix, vagina, vulva, urinary tract, rectum, anus, and postmenopausal bleeding were excluded from the study.

Patients were categorized based on histopathology and imaging results into the following groups: polyp (AUB - P), adenomyosis (AUB - A), leiomyoma (AUB - L), malignancy and hyperplasia (AUB - M), coagulopathy (AUB - C), ovulatory dysfunction (AUB - O), endometrial (AUB - E), iatrogenic (AUB - I), and not otherwise classified (AUB - N). The

beginning of the pandemic was considered to be March 2020, when the first case was announced in our country.

### Statistical Analysis

Data analysis was performed using SPSS statistic software (version 27; IBM Corporation, New York, NY). The pre-pandemic and pandemic period groups were compared using a Z-test for binary proportions, considering percentile distributions within the groups. A p - value of < 0.05 was considered statistically significant.

## Results

A total of 1045 patients were included in the analysis, with 401 patients before the pandemic and 644 patients during the pandemic. The average age of the 1045 participants was  $47.37 \pm 8.718$  years, and the mean parity was  $3.78 \pm 1.409$ . The mean BMI was  $29.6 \pm 5.4$ .

According to the FIGO's classification terminology, before the pandemic, 55 (13.7%) patients were diagnosed with polyps (AUBP), while during the pandemic, 68 (10.6%) patients were diagnosed with polyps (AUBP) ( $p = 0.123$ ,  $p > 0.05$ ). Before the pandemic, 32 (8.0%) patients had adenomyosis (AUB - A), and during the pandemic, 33 (5.1%) patients had adenomyosis (AUB - A) ( $p = 0.062$ ,  $p > 0.05$ ). Before the pandemic, 125 (31.2%) patients had leiomyoma (AUB - L), and during the pandemic, 165 (25.6%) patients had leiomyoma (AUB - L) ( $p = 0.051$ ,  $p > 0.05$ ). Before the pandemic, 8 (2.0%) patients had malignancy and hyperplasia (AUB - M), while during the pandemic, 9 (1.4%) patients had malignancy and hyperplasia (AUB - M) ( $p = 0.459$ ,  $p > 0.05$ ). These four categories belong to the components of the PALM group, which are structural entities that can be visually measured with imaging methods and / or histopathology (before the pandemic 220, 54.86%, during the pandemic 275, 42.70%).

No patients were defined with coagulopathy (AUB - C). Before the pandemic, 123 (30.7%) patients had ovulatory disorders (AUB - O), and during the pandemic, 239 (37.1%) patients had ovulatory disorders (AUB - O) ( $p = 0.033$ ,  $p < 0.05$ ). Before the pandemic, 55 (13.7%) patients had endometrial issues (AUB - E), while during the pandemic, 123 (19.1%) patients had endometrial issues (AUB - E) ( $p = 0.024$ ,  $p < 0.05$ ). Before the pandemic, 1 (0.2%) patient had iatrogenic factors (AUB - I), and during the pandemic, 3 (0.5%) patients had iatrogenic factors (AUB - I) ( $p = 0.582$ ,  $p > 0.05$ ). Before the pandemic, 2 (0.5%) patients were not classified (AUB - N), and during the pandemic, 4 (0.6%) patients were not classified (AUB - N) ( $p = 0.802$ ,  $p > 0.05$ ). These five categories belong to the components of the COEIN group, which are related to nonstructural entities (before the pandemic 181, 45.13%, during the pandemic 369, 57.29%). (Table I)

**Table 1:** Pre-pandemic and during-pandemic causes of AUB according to the PALM COEIN classification

	Total n (%)	Before The Pandemic n (%)	During The Pandemic n(%)	p
P	123 (11.8%)	55 (13.7%)	68 (10.6%)	0.123
A	65 (6.2%)	32 (8.0%)	33 (5.1%)	0.062
L	290 (27.8%)	125 (31.2%)	165 (25.6%)	0.051
M	17 (1.6%)	8 (2.0%)	9 (1.4%)	0.459
C	0 (0.0%)	0 (0.0%)	0 (0.0%)	
O	362 (34.6%)	123 (30.7%)	239 (37.1%)	<b>0.033</b>
E	178 (17.0%)	55 (13.7%)	123 (19.1%)	<b>0.024</b>
I	4 (0.4%)	1 (0.2%)	3 (0.5%)	0.582
N	6 (0.6%)	2 (0.5%)	4 (0.6%)	0.802
Total	1045 (100%)	401 (100%)	644 (100%)	

## Discussion

In this study, we investigated whether there were any changes in factors causing AUB based on the PALM - COEIN classification during the COVID - 19 pandemic. We found a significant increase in ovulatory disorders and endometrial causes during the COVID - 19 pandemic compared to the pre - pandemic period. To the best of our knowledge, our study is the first of its kind in the literature. Increased stress factors during the COVID - 19 pandemic, vaccinations, and direct inflammation of the ovaries and endometrial tissue appear to be the primary reasons for menstrual cycle disruptions. This clearly indicates that ovulatory disorders and endometrial causes, now classified under the COEIN heading, were affected during the COVID - 19 pandemic period (13).

Menstruation, tightly regulated by the hypothalamic - pituitary - ovary axis, reflects women's overall physical condition and is influenced by environmental factors (7). Various factors can lead to ovulatory disorders, including a range of endocrine disorders such as polycystic ovary syndrome (PCOS), hyperprolactinemia, hypothyroidism, iatrogenic factors that act through steroid hormone use, or dopamine metabolisms, such as phenothiazines or tricyclic antidepressants, systemic diseases like chronic liver and kidney disease, stress, eating disorders, and intense exercise (14). Factors that affect menstrual cycles, such as stress, weight changes, diet, and medication use, have been influenced by the significant changes in our lives during the COVID - 19 pandemic. These changes affect the hypothalamic - pituitary axis, resulting in an imbalance between estrogen and progesterone, leading to AUB (15). It is known that the entire menstrual cycle changed during the COVID - 19 pandemic due to these psychosocial and environmental stress factors (13).

Studies have shown that menstrual irregularities were reported shortly after hepatitis B and typhoid vaccinations (16,17). Similarly, during the COVID - 19 pandemic, increases in menstrual cycle length were observed shortly after vaccination (13). In the United Kingdom, more than 40,000 cases of

AUB were identified after administering 50 million doses of the COVID - 19 vaccine to women (18). Different studies have reported that approximately one - third of vaccinated women experienced early - stage AUB (11,19,20). This situation develops through various mechanisms, including immunological effects on estrogen and progesterone and systemic inflammatory responses on the ovaries and endometrium (15). The menstrual cycle is tightly regulated by inflammatory and immune mediators, especially characterized by matrix metalloproteinases. Through this mechanism, the necessary breakdown and disruption of the endometrial tissue for menstruation occurs. In addition, immune cell activation can contribute to severe menstrual bleeding (21). The immune response induced by COVID - 19 vaccines may temporarily affect the hypothalamic - pituitary - ovary axis, leading to menstrual disorders. This suggests that excesses during the COVID - 19 pandemic may be directly related to menstrual irregularities (13).

Acute viral infections can cause changes in menstrual characteristics through mechanisms such as direct inflammation of the ovaries and immune alterations (8,9). Direct inflammation of the ovaries is highly likely during the COVID - 19 pandemic (13). Inflammatory processes in the ovaries lead to functional and reproductive problems. In a study by Ding et al. (22), a significant decrease in ovarian reserve (serum AMH) was found in COVID - 19 patients compared to women of the same age who were not infected. In our study, we found an increase in the ovulatory disorders group during the pandemic period. It does not seem entirely accurate to explain this solely by an increase in stress. Similarly, disruptions in endometrial hemostatic mechanisms are possible causes of abnormal uterine bleeding. Increases in the production of vasodilatory substances such as prostaglandin E2 and prostacyclin or defects in the production of local vasoconstrictors such as prostaglandin F2  $\alpha$  and endothelin - 1, as well as an increase in plasminogen activators resulting in increased thrombolysis, can lead to heavy menstrual bleeding. In addition, a possible defect in endometrial inflammation or repair mechanisms secondary to infection can lead to intermenstrual or prolonged bleeding.



During the COVID - 19 pandemic, not only direct inflammation of the ovaries but also direct inflammation of the endometrial tissue can lead to AUB through these pathways (23-25).

The retrospective nature of this single - center study may restrict the applicability of the findings to broader populations, and an extended follow - up period could have provided additional insights. The strength of this study lies in its distinction as, to the best of our knowledge, the first of its kind in the literature. Additionally, its large cohort size enhances the robustness of the findings, providing valuable insights into the subject matter and paving the way for future research.

In conclusion, our study highlights significant changes in the factors contributing to abnormal uterine bleeding (AUB) during the COVID - 19 pandemic, with a notable increase in ovulatory disorders and endometrial causes. These changes can be attributed to several factors, including the stress associated with the pandemic, the potential impact of COVID - 19 vaccinations, and direct inflammation of the ovaries and endometrial tissue. The disruption of the menstrual cycle during this period reflects the complex interplay of psychosocial, environmental, and physiological stressors that have altered the functioning of the hypothalamic - pituitary - ovarian axis. While stress and vaccination - induced immune responses have been identified as primary contributors, the direct inflammation of reproductive tissues may also have played a crucial role in the observed increase in AUB cases. Our findings underscore the importance of considering the broader effects of the pandemic on reproductive health, with implications for future research on how viral infections and immunological factors influence menstrual health. Given the limitations of our study, further research is needed to explore the long - term impact of the COVID - 19 pandemic on menstrual health and to better understand the underlying mechanisms at play.

#### *Declarations*

*Ethics approval and consent to participate: All participants signed informed written consent before being enrolled in the study. The study was reviewed and approved by the ethics committee of the Baskent University Institutional Review Board (Ethics approval reference number: KA23/11 date 10.01.2023). All procedures were performed according to the Declaration of Helsinki.*

*Availability of data and materials: The data supporting this study is available through the corresponding author upon reasonable request.*

*Competing interests: The authors declare that they have no competing interests.*

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*Authors' Contributions: OB and HC contributed to the study conception and design. Data collection was performed by OB, SA, and GDD. Statistical analysis was performed by OB and KB. The first draft was written by OB and KB. Critical reading was performed by GDD and HC. All authors read*

*and approved the final manuscript.*

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