Original Article

Evaluating Clinical Features in Intracavitary Uterine Pathologies among Vietnamese Women Presenting with Peri-and Postmenopausal Bleeding: A Bicentric Observational Descriptive Analysis

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ABSTRACT

Background: Intracavitary uterine pathologies (IUPs) may be resulting in vaginal bleeding in perimenopausal and postmenopausal women. Especially, malignant disease needed to be investigated due to its adverse impact on the quality of mid-life women as well as the burden of health-care costs in low- and middle-income countries such as Vietnam. **Objective:** Thereby, through this study, we aimed to assess the major clinical features of IUPs in women with perimenopausal and postmenopausal bleeding women. **Materials and Methods:** This was a cross-sectional observational study at Hue University Hospital and Hue Central Hospital from June 2016 to June 2019. The study enrolled 150 women above 40 years old involving with intrauterine bleeding. **Results:** The mean age of the study population was 51.51 ± 7.65. The most common symptom in perimenopausal women was menorrhagia, up to 62.2% of cases. In addition to intrauterine bleeding, there were 54.7% of cases had at least one other functional symptom, they were pale skin (35.9%), and lower abdominal pain (31.3). Endometrial hyperplasia (EH) was the most common pathology in both groups with perimenopausal and postmenopausal bleeding (PMB), respectively, 66.7% and 51.7%. In PMB group, endometrial cancer (EC) occupied approximately 38.3% following EH. Our study revealed age, menstrual characteristics, and diabetes in relation to malignant disease. Other factors seemed to be less associated with EC. **Conclusions:** Menorrhagia was the most common type of abnormal uterine bleeding in perimenopausal women. Besides vaginal bleeding, others symptoms such as pale skin, pelvic pain, and fatigue were also common. Length day and blood loss before hospitalization in perimenopausal women were greater significantly than that in postmenopausal women. Age, menstrual characteristics, and diabetes increased the risk of EC in women with PMB.

KEYWORDS: *Abnormal uterine bleeding, clinical features, endometrial cancer, intracavitary uterine pathologies, perimenopause, postmenopause, Vietnamese women*

INTRODUCTION

The stage of menopause refers typically to perimenopause, menopause, and postmenopause and marks a transition's period in women's life, including overall health.[1] Nature menopause is defined as the absence of menstrual period in 12 consecutive months. It occurs in the late 40s to early 50s, varying from this race to another race.[2] This issue does not refer to hormonal therapy, and primary ovarian insufficiency.

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Around the mid-life period, women usually experience several changes in mental, psychological health and overall body, due to decrease of hormonal level as well as ovarian function.[3-5] Hormonal changes may lead to menstrual disorders and cause vaginal bleeding. However, vaginal bleeding may arise from the vaginal tract, cervical abnormalities, and uterus. Hemorrhage from vagina and cervix could be assessed by visual examination via speculum. Uterine bleeding may be originated from either menstrual disorders or from uterine pathologies. Therefore, uterine corpus bleeding during this stage needed to be investigated carefully.[6]

Abnormal uterine bleeding (AUB) is defined as menstrual flow outside of normal volume, duration, regularity, or frequency.[7] AUB affects to 10%-30% of women during the reproductive period. One-third of outpatients visit to the gynecologist for AUB, and it accounts for more than 70% of all gynecological visits in the perimenopausal and postmenopausal years. AUB patterns include menorrhagia, metrorrhagia, polymenorrhea, and oligomenorrhagia.[8,9] In an effort to create a universally accepted system of nomenclature to describe uterine bleeding abnormalities in reproductive-aged women, a new classification system (polyp, adenomyosis, leiomyoma, malignancy and hyperplasia, coagulopathy, ovulatory dysfunction, endometrial, iatrogenic, and not yet classified), known by the acronym PALM–COEIN, was introduced in 2011 by the International Federation of Gynecology and Obstetrics (FIGO).[10] The American College of Obstetricians and Gynecologists supports the adoption of the PALM–COEIN nomenclature system developed by FIGO to standardize the terminology used to describe AUB.[8] However, these terms have remained new at our hospitals as well as at health care centers around the world due to its novelty. Among abnormalities leading to chronic intrauterine bleeding, structural etiologies play an important part requiring to have more clinical exploratory modalities, up to 20%–30% associated with polyps in structural causes.[6,11] Especially, endometrial cancer (EC) is responsible for mortality among the elderly population, increasing longevity, and thus, needing an adequate awareness from health care worldwide.[12,13]

Until today, we have had many appropriate modalities to evaluate intrauterine bleeding in perimenopausal and postmenopausal women including noninvasive and invasive procedures. These modalities may be ultrasound, saline infusion sonography, computerized tomography scanner, magnetic resonance imaging, hysteroscopy, endometrial biopsy, etc.[14-18] However, some modalities remain expensive for assessment in low- and middle-income countries such as Vietnam. Meanwhile,

the physician can firstly approach to initial features, evaluate carefully clinical symptoms, and classify the degree of anemia prior to investigate by additional diagnostic modalities as ultrasound, biopsy, and surgical procedures.[19-21] Based on well-known risk factors such as body mass index (BMI), diabetes, and ages, we also develop a model combined with sonographic findings for accurately predicting EC and making a decision for further invasive procedures.[22-25] Up to our knowledge, the findings about clinical features in relation to IUPs in peri-and postmenopausal bleeding women have remained limited in Vietnam; therefore, our purposes were to investigate this entity and contribute to the literature some risk factors relating to EC in the Vietnamese population.

MATERIALS AND METHODS
Study design and population

This observational descriptive study was conducted according to the ethics committee of our university and was approved by our institutional review board with IRB approval 1435/QĐ-ĐHYD. The study was conducted in compliance with the ethical standards of the responsible institution on human subjects as well as with the Helsinki Declaration. All female patients gave us written informed consent. This study was done at Hue Central Hospital and Hue University Hospital between June 2016 and June 2019 [Figure 1]. Convenience sampling technique was used.

Inclusion criteria included all the women eligible more than 40 years old complaining with AUB.

Exclusion criteria included bleeding related to pregnancy, hormone replacement therapy, tamoxifen,
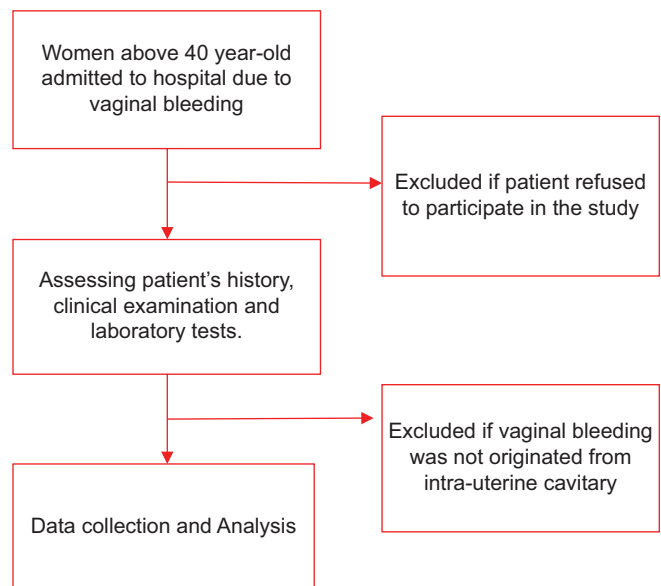

Figure 1: Study flowchart

coagulation disorders, bleeding not originated from the uterine cavity, abnormalities associated with the cervix, iatrogenic bleeding, and lack of information on the study protocol.

Data collection

Overall, a total of 150 women were recruited and participated in this study.

All the patients were submitted to the following: thorough disease's history, general examination, gynecological examination, cervical cytology (Pap smear), and laboratory investigations (complete blood count, liver function tests, kidney function tests, and a coagulation profile).

Followed by some routinely exploratory examinations, all the patients underwent interventional procedures such as endometrial biopsy, hysteroscopy, myomectomy, or hysterectomy. These indications were decided following the medical protocol applied currently at our hospital.

Data were recorded from the patient's file and based on patient interview with qualitative responses, classified following variabilities:

- Continuous variables include age, age at first menarche, age at menopause, total menopausal years bleeding duration before hospitalization (days), and time with first intrauterine bleeding (months)
- Categorical variables include:
  - Amount of blood loss during the menstrual cycle may be evaluated, followed by several methods such as pictorial blood loss assessment charts, alkaline hematin technique, and hemoglobin concentration.[9] However, we have not found a suitable tool for perimenopausal and postmenopausal bleeding (PMB) women in the literature. Moreover, Vietnamese women do not notice regularly blood loss during their menstrual period by their routine calendar. Therefore, we assessed initially following patient self-evaluation, based on the number of sanitary pads changed per day compared to their previous periods on the clinic aspect. According to perimenopausal women: slight (1 pad/day), moderate (2–3 pads/day), and heavy (≥4 pads/day). Regarding postmenopausal women: slight (≤1 pad/day), moderate (2 pads/day), and heavy (≥3 pads/day)
  - Functional signs were recorded on clinical examination
  - BMI following classification of the World Health Organization[26]
  - Diabetes following the standard of the American Diabetes Association (2019)[27]
  - Hypertension following the diagnosis of the United States Joint National Committee 7[28]

- History of regular menstrual cycle, history of dilation and curettage (D & C), and obstetric history (gravidity, parity).

The histopathological result was collected within 1–2 weeks after surgical intervention.

Statistical analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 20.0. Statistical tests were used according to the distribution of data, and $P < 0.05$ was considered statistically significant.`

RESULTS

Enrolment of 150 women, of which 60 women were in the postmenopausal period and 90 women were in the perimenopausal period. The mean age of the study was 51.51 ± 7.65, perimenopausal age was 47.21 ± 3.78, and postmenopausal women were 57.97 ± 7.43. The common age group was 45–49 (47.8%) and 50–54 (36.7%), respectively [Table 1]. According to perimenopausal women presenting as AUB, menorrhagia occupied 56/90 cases [Figure 2]. In our study, the most common surgical procedures performed were dilation and curettage

Table 1: Age distribution in perimenopausal and postmenopausal bleeding women

| Age group | Women with intrauterine bleeding | | Total, n (%) |
	Perimenopause, n (%)	Postmenopause, n (%)	
40-44	24 (26.7)	0	24 (16.0)
45-49	43 (47.8)	3 (5.0)	46 (30.7)
50-54	23 (23.5)	22 (36.7)	45 (30.0)
55-59	0	15 (25.0)	15 (10.0)
≥60	0	20 (33.3)	20 (13.3)
Total	90 (100.0)	60 (100.0)	150 (100.0)
$\bar{X}$±SD	47.21±3.78	57.97±7.43	51.51±7.65

SD: Standard deviation

Table 2: Functional symptoms accompanied with abnormal intrauterine bleeding

Functional features	Frequency (n)	Percent (%) [a]	Percent (%) [b]
Pale skin	47	35.9	57.3
Fatigue/dizziness	22	16.8	26.8
Low abdominal pain	41	31.3	50.0
Fever/infection	1	0.8	1.2
Anorexia/loss of weight	4	3.1	4.9
Vaginal discharge	6	4.6	7.3
Constipation	10	7.6	12.2

[a]Rate of functional feature over total of functional symptoms accompanied with abnormal intrauterine bleeding (total: 131), [b]Rate of every functional feature among total of cases which had functional symptoms accompanied with abnormal intrauterine bleeding (82/150 cases)
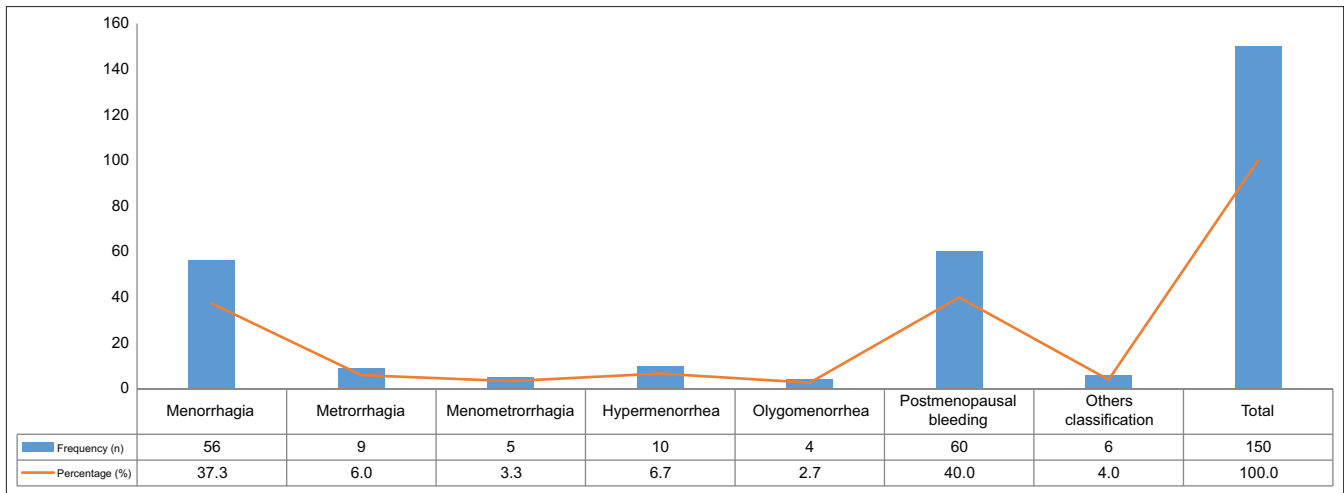
Figure 2: Type of intrauterine bleeding

combined with Karman cannula for endometrial sampling (95/150 patients). Among 150 cases, 68 patients had no other signs besides vaginal bleeding (45.3%). The most popular symptoms accompanied by AUB were pallor and pelvic pain, which occupied 35.9% and 31.3%, respectively [Table 2]. The amount of blood loss classified by mild-severe level according to self-evaluation of patient in perimenopausal group was much greater than that in postmenopausal group, respectively, 57.1% vs 6.7%. Almost cases were hospitalized below 3 months, only a few of women were admitted to the hospital more than 3 months. Mean length days of vaginal bleeding prior to hospitalization was longer in perimenopausal group than that in postmenopausal group [Table 3]. The diabetes rate in the malignant group was higher than this in the benign group, 24.0% versus 1.6%, significantly. It had a relationship between diabetes and EC with odds ratio (OR): 19.42, 95% confidence interval (CI): 3.65–103.34. The obesity rate in the malignant group was greater than this in the benign group, 24.0% vs. 14.3%, but not significantly. Regular menstrual period was also related to EC, hypertension had no association with EC in our study, $P > 0.05$ [Table 4]. In the present study, the mean age in the malignant group was greater than that in the benign group, significantly. Age at first menarche was earlier in the malignant group with $P < 0.05$. However, gravity, parity, body max index, previous history of dilation and curettage (D&C) were not different between both groups significantly [Table 5].

DISCUSSION

In our study, the mean age of female patients was 51.51 ± 7.65 ranging from 40 to 80 years. The mean age of perimenopausal bleeding group in our study was older than that in the study of Mayuri et al., respectively, 47.21 ± 3.78 (years) vs 44.77 ± 4.47 (years).[29] The

Table 3: Features of intrauterine bleeding

Bleeding characteristics	Perimenopause, n (%)	Postmenopause, n (%)
Volume of blood loss		
Mild	39 (43.3)	56 (93.3)
Moderate	19 (21.5)	3 (5.0)
Heavy	32 (35.6)	1 (1.7)
Total	90 (100.0)	60 (100.0)
Bleeding duration		
<3 months	81 (89.2)	56 (93.4)
3-6 months	5 (5.4)	2 (3.3)
>6 months	5 (5.4)	2 (3.3)
Total	90 (100.0)	60 (100.0)
Duration of intrauterine bleeding prior to hospitalization, $\bar{X}$±SD (days)	19.04±25.08	14.63±33.97

SD: Standard deviation

Table 4: Association between diabetes, hypertension, obesity, menstrual period with benign and malignant group

| Group	Benign		Malignant		P	OR
Disease	n	%	n	%		95% CI$_{OR}$
Diabetes						
Yes	2	1.6	6	24.0	<0.0001	19.42
No	123	98.4	19	76.0		(3.65-103.34)
Hypertension						
Yes	17	13.6	5	20.0	0.409	1.59
No	108	84.4	20	80.0		(0.53-4.80)
Obesity						
Yes	17	13.6	6	24.0	0.188	0.50
No	108	86.4	19	76.0		(0.17-1.43)
Regular period						
Yes	94	75.2	24	96.0	0.02	7.92
No	31	24.8	1	4.0		(1.03-60.94)

*P*-value archived from Chi-square test

Table 5: Age, age at first menarche, gravity, parity, BMI, history of previous D and C between benign and malignant group

| Group Characteristics	Benign X̄±SD (min-max)	Malignant X̄±SD (min-max)	Total X̄±SD (min-max)	P*
Age (year)	49.94±6.54 (40-78)	59.32±8.08 (46-80)	51.50±7.65 (40-80)	< 0.0001
Age at the first menarche (years-old)	14.14±1.40 (10-21)	13.32±1.75 (11-18)	14.01±1.49 (10-21)	0.03
Gravidity	3.67±1.83 (0-10)	3.40±1.80 (0-6)	3.63±1.82 (0-10)	0.5
Parity	3.01±1.47 (0-7)	2.72±1.57 (0-6)	2.96±1.48 (0-7)	0.38
Previous history of D&C (times)	0.71±0.83 (0-3)	0.68±0.79 (0-3)	0.84±1.03 (0-3)	0.47
Body max index (kg/m²)	17.26±2.15 (11.94-24.53)	17.80±2.66 (14.19-26.69)	17.35±2.24 (11.94-26.69)	0.27

*P-value archived from Student's T-test
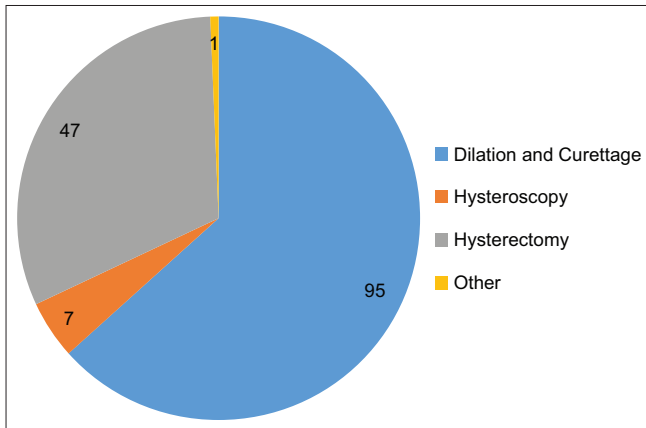
Figure 3: Frequency of surgical procedures
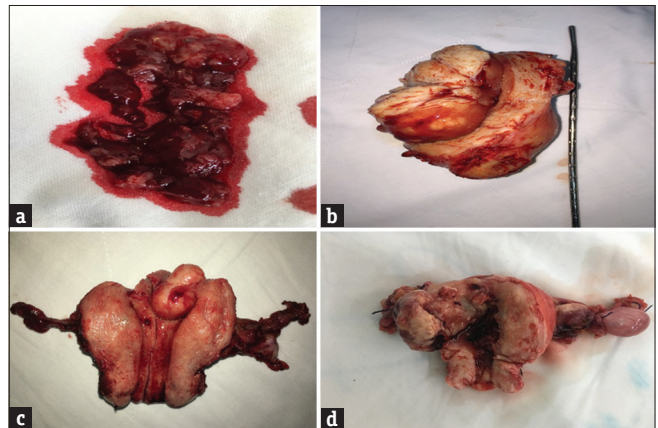
Figure 4: Macroscopic specimen images of intracavitary uterine pathologies in the study including endometrial hyperplasia (a), submucosal fibroids (b), pedunculated endometrial polyp (c), and endometrial cancer (d)
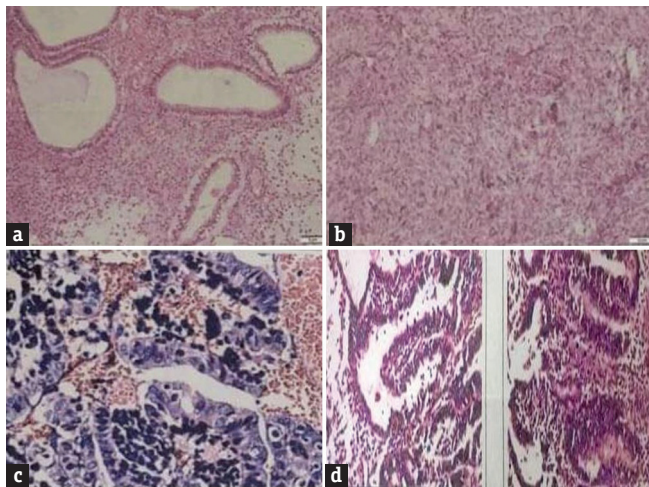
Figure 5: Histopathological examination of tissue with hematoxylin and eosin stained section (10x, 40x) in the present study including: (a) Endometrial hyperplasia, (b) Submucosal fibroid, (c) Endometrial polyp, and (d) Endometrial cancer

average age of postmenopausal women with AUB was 58.03 ± 7.44, similar to the study of Alcázar et al. and Bouzid et al.[30,31] Table 1 shows that the group age of menopause accounted for the majority of group aged 50–54 years (35.6%), similar to the result of Bano et al.[32]

Recently, FIGO has recommended to use new terminologies to describe types of AUB; hence, in our study, we still used previous terms to describe the types of AUB. Since the previous terminologies have remained common at our hospital and around the world.[33] In the present study, PMB occupied up to 40.0%, menorrhagia accounted for 56/90 cases in perimenopausal bleeding group, and 37.3% in the overall study, followed by hypermenorrhea and metrorrhagia [Figure 2]. Other types of AUB such as bleeding after sex, oligomenorrhea, and spotting bleeding only accounted for a small percentage, about 4.0%. Despite existing difference in study population, generally, menorrhagia is still the common type of bleeding in perimenopausal women with AUB.[34-36] Dilation and curettage by Karman cannula is considered as an adequate method for the hemorrhagic treatment and endometrial sampling biopsy, thus, almost cases underwent this interventional procedure in our study [Figure 3].[37] According to Gupta et al., the use of Karman cannula resulted in less pain and is a much cheaper option in comparison to Pipelle.[38] Following the current protocol applied at our hospital, several cases were indicated to hysterectomy following the histopathological endpoint in suspicion with malignant disease and we analyzed subsequently based on the last result of the interventional procedure [Figures 4 and 5].

In addition to intrauterine bleeding, there were 82 over 150 cases with at least one other symptom. Among them, pallor (35.9%), abdominal lower pain (31.3%), and fatigue/dizziness (16.8%) were three common accompanying symptoms. Other functional symptoms such as urinary disorders, fever, and weight loss were less common [Table 2].

In the present study, approximately 21.5% of perimenopausal women self-evaluated moderate blood loss compared with 5.0% of postmenopausal women. Similarly, 35.6% of perimenopausal women self-assessed blood loss more than the average menstrual cycle compared with 1.7% in postmenopausal women. In the study of Jadoon et al (2019), postmenopausal bleeding was mainly spotting and light bleeding accounted for 81.0%, approximate to our study was 93.3% and the majority was recurrent.[39] The time to detect the first intrauterine bleeding and the duration of bleeding days before hospital admission in the perimenopausal group was also longer than in postmenopausal women [Table 3]. After a long period of amenorrhea, postmenopausal women were often more concerned about vaginal bleeding than perimenopausal women. However, almost patients in our study were hospitalized under 3 months of bleeding (93.4%), only a few cases admitted after 6-12 months, the maximum time duration was 16 months, similar to the study of Takreem et al.[40] Following Aboul-Fotouh, the mean time duration was 7.6 ± 3.5 days, varying from 1 to 30 days, similar to Wilailak, and shorter than that in our study (14.63 ± 33.97 days).[41,42] This result revealed that some Vietnamese women in the perimenopausal period were less concerned with vaginal bleeding until the symptoms of anemia caused anxiety.

Among the structural causes of intrauterine bleeding, no specific factor has been found to be contributed to the development of polyps or endometrial fibroma. However, risk factors have been studied intensively and are believed to play an important role in increasing the risk of malignancy of EC.[9] Using the Chi-square test, there was a difference between malignant and benign groups in the general sample of diabetes disease, 24% versus 1.6%, with $P < 0.05$, OR: 19.42, 95% CI: 3.65–103.34. In a large prospective cohort study in the United Kingdom (2012) by Burbos et al., 3047 women with PMB revealed that BMI, diabetes, and hypertension were statistically significantly higher in the malignant group than in the benign group, similar to the report of Fatima et al.[43,44] BMI in the malignant group was greater than in the benign group also reported in many studies in the literature.[22,24,30,45,46] According to Wise et al., BMI should be the first stratification in the decision to perform endometrial biopsy and/or to refer the secondary gynecological service.[21] As comparing with our results, the percentage of BMI ≥25 (kg/m²) in the cancer group was greater than in the benign group (24.0% vs. 13.6%), but there was no statistical significance ($P > 0.05$). BMI in our study was lower than in other studies worldwide.[21,47] There was no statistically significant difference between the two groups of pathologies due to probable differences in racial characteristics. Besides, we found that regular menstrual period may be also related to EC in our study. Conversely, Wang et al. reported that irregular menstrual cycles are more likely related to increased risk of EC.[48] Thus, we need more researches to verify this issue [Table 4].

Table 5 shows that the mean age in the overall sample between malignant and benign groups was 59.32 ± 8.08 compared with 49.94 ± 6.54. There was a statistically significant difference with $P < 0.0001$. In postmenopausal bleeding group, the mean age between two pathological groups was not different significantly ($P=0.05$), different from the results of Ashour et al., and Madkour et al., who found the mean age in the malignant group higher than that in the benign group. Thus, these authors concluded that the older age, the more risk related to EC.[49,50] Probably, these studies were not similar to our study in the condition of sample size and frequency of malignancies. Moreover, our study found that gravidity, parity, body max index, previous history of dilation and curettage were not in association with EC.

Age at the first menstrual period was not statistically significant in postmenopausal women, between malignant and benign groups, 13.32 ± 1.75 compared with 14.14 ± 1.40 with $P > 0.05$. Apart from other studies found that the early first menarche was more related to EC than in the group of late menarche.[40]

Strengths and limitations

This study has been interesting in analyzing the clinical features relating to IUPs in peri-and postmenopausal bleeding women, moreover, this has been the first study mentioning on this issue in Vietnam.

However, the sample size was still small without control group, especially in the malignant group. Almost all data was based on patient's responses. This qualitative study did not include the clinical features in the patients without histopathological examination such as endometrial atrophy, endometritis, or normal endometrium, etc, thus leading to the bias study. Furthermore, due to limited number cases of endometrial cancer in perimenopausal bleeding group, our study could not analyze intensively the clinical features and the risk factors for endometrial cancer in subgroup.

Conclusions

Menorrhagia was the most common type of AUB in perimenopausal women. Besides hemorrhagic symptom leading to anxiety, pale skin, lower abdominal pain, and tiredness were also common. Length day and blood loss before hospitalization in perimenopausal women were greater significantly than that in postmenopausal women. Age, menstrual characteristics, and diabetes increased the risk of EC in PMB group. Other factors were less associated with EC.

Author's contributions

Phuc Nhon Nguyen was involved for for conceptualization, methodology, investigation, software, data curation, writting, editing, and revising the manuscript. Van Tuan Nguyen was responsible for administrative procedures. Both authors read and approved the fnal manuscript.

Conflicts of interest

There are no conflicts of interest.

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