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Exploring risk factors and management strategies for endometrial premalignant/malignant lesions in women with abnormal uterine bleeding: A retrospective cohort study

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Ethics Committee Approval
The study was approved by Bursa Yuksek Ihtisas Training and Research Hospital Clinical Research Ethics Committee (Approval No: 2011-KAEK-25 2023/08-14).
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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Abstract

Background/Aim: Abnormal uterine bleeding (AUB) in women can often be attributed to a range of underlying factors, including endometrial premalignant and malignant lesions. However, despite the prevalence and potential severity of these lesions, the specific risk factors contributing to their development have not been fully explained. This study aims to explore the risk factors linked to these lesions and to elucidate the corresponding management strategies, filling a crucial gap in our understanding of the underlying causes of AUB.

Methods: This retrospective cohort study was conducted among women presenting with AUB and undergoing endometrial biopsy at a gynecology clinic between July 2018 and January 2022. We recorded patients' demographic and clinical characteristics, ultrasonographic findings, and histopathological results of endometrial biopsies. Excluded from the study were patients under 30 years old, pregnant women, those with biopsy results from another center, individuals diagnosed with cancers other than endometrial cancer, cases of insufficient endometrial biopsies, and patients with missing data. The included patients were categorized into two groups: benign and premalignant/malignant, based on histopathological results, and subsequently compared using clinicodemographic findings. Logistic regression analysis was conducted to identify significant risk factors for premalignant/malignant endometrial lesions. We assessed the predictive capacity of endometrial thickness (ET) for premalignant/malignant lesions through receiver operating characteristic (ROC) analysis.

Results: A total of 391 patients were analyzed, with a mean age of 50.9 (7.7) years. Among these patients, 89.3% (n=349) were classified as benign, while 10.7% (n=42) exhibited premalignant/malignant lesions. The premalignant/malignant group displayed higher age and BMI compared to the benign group (55.83 [10.55] vs 50.3 [7.6], P<0.001 and 29.17 [3.40] vs 27.73 [3.67], P=0.018, respectively). Logistic regression analysis identified age, BMI, and ET as significant risk factors associated with premalignant/malignant endometrial lesions. ROC analysis for predicting premalignant/malignant lesions using ET yielded cut-off values of 10.5 mm for premenopausal women (sensitivity 62.5%, specificity 58.7%, AUC [95% CI]: 0.688 [0.56-0.80], P =0.012) and 8.5 mm for postmenopausal women (sensitivity 88.5%, specificity 70.2%, AUC [95% CI]: 0.854 [0.78-0.92]; P<0.001).

Conclusion: In summary, our findings shed light on the pivotal role of age, BMI, ET, and menopausal status in tailoring management strategies for patients with AUB, underscoring the importance of individualized approaches in enhancing patient care. However, definitive conclusions warrant multi-center prospective investigations to validate these findings in a larger population.

Keywords: uterine bleeding, endometrial carcinoma, endometrial hyperplasia, postmenopausal period, pre-menopause

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Introduction

Endometrial cancer (EC) is an increasingly prevalent gynecological malignancy worldwide [1]. While its incidence rates peak in the 60s, it can also manifest before the age of 40 [2]. The primary symptom of EC is abnormal uterine bleeding (AUB), prompting approximately 90% of cases to seek medical attention [3]. Abnormal bleeding patterns associated with EC include intermenstrual bleeding, heavy bleeding, frequent menstruation, and postmenopausal bleeding [3,4]. However, similar bleeding patterns can arise from benign conditions. In cases of AUB, differential diagnosis between cancer and benign causes necessitates histopathological confirmation via endometrial biopsy, curettage, or hysterectomy specimens. Consequently, many women are subjected to unnecessary invasive diagnostic procedures due to cancer risk concerns. Thus, predicting malignancy risk has gained paramount importance in endometrial assessments. Despite ongoing research on markers and diagnostic tools for high-risk prediction, a global consensus on the optimal clinical management of endometrial evaluations remains elusive [5-7].

This retrospective study aims to evaluate risk-based approaches for diagnosing premalignant or malignant endometrial lesions in women presenting with abnormal uterine bleeding. By assessing the efficacy of these approaches, this study seeks to enhance diagnostic accuracy, minimize unnecessary procedures, and contribute to a more informed consensus on managing endometrial assessments in clinical practice.

Materials and methods

This retrospective cohort study was conducted at the Bursa Gemlik State Hospital's Obstetrics and Gynecology Clinic. It involved patients who presented to the gynecology and obstetrics outpatient department between July 2018 and January 2022 and had undergone endometrial biopsy. Ethical approval was obtained from Bursa Yuksek Ihtisas Training and Research Hospital Clinical Research Ethics Committee (Approval No: 2011-KAEK-25 2023/08-14). Throughout the study, adherence to the principles of the Helsinki Declaration was ensured.

A total of 427 patients who were over 30 years of age with complaints of AUB and who had undergone endometrial biopsy were reviewed for the study. Demographic data, including age, height, weight, pregnancy history, medical history, physical examination findings, pre-biopsy ultrasound results, and laboratory findings were extracted from electronic medical records. Patients with AUB and documented endometrial biopsy histopathology results were included, while those under 30 years of age, pregnant women, patients with biopsy results reported from another center, individuals diagnosed with cancers other than endometrial cancer, and cases of insufficient endometrial biopsies were excluded. Additionally, patients for whom data retrieval was challenging were excluded from the study to mitigate potential information bias.

In this retrospective study, the sample size was determined based on the available data from the study period. The study aimed to include all eligible cases within the specified timeframe to maximize the available information. While a predetermined sample size calculation was not feasible due to the retrospective nature of the study, efforts were made to include a comprehensive dataset of patients meeting the inclusion criteria. The study size was determined by the number of eligible cases that met the criteria for data availability, enabling us to conduct a meaningful analysis of the research objectives.

Included patients (n=391) were categorized based on histopathological results and divided into two groups: benign and premalignant/malignant. The premalignant/malignant group comprised cases with hyperplasia with or without atypia, endometrial intraepithelial neoplasia (EIN), and endometrial carcinoma. The benign group included cases with findings, such as endometrial fragments, proliferative endometrium, secretory endometrium, endometrial polyps, endometritis, atrophy, and metaplasia. Gynecologic pathologists made the histopathological diagnoses.

Transvaginal ultrasonography (TVUS) was performed before the procedure to measure endometrial thickness (ET) in all patients. Endometrial biopsy samples were obtained using a No. 4 Karman cannula via therapeutic curettage in an outpatient setting. Patients who had not experienced menstruation for over a year were classified as postmenopausal. AUB patterns were classified according to the International Federation of Gynecology and Obstetrics (FIGO) [8]. Bleeding occurring during the regular menstrual cycle was referred to as intermenstrual bleeding, while bleeding that significantly affected the quality of life was categorized as heavy menstrual bleeding. Irregular bleeding that was not cyclic or consistent, but had a normal amount, was defined as irregular bleeding. Bleeding patterns were categorized as postmenopausal bleeding, intermenstrual bleeding, heavy menstrual bleeding and irregular bleeding.

The primary outcome was the incidence of premalignant/malignant lesions. The secondary outcome involved assessing the relationship between endometrial premalignant/malignant lesions and the variables under consideration.

Statistical analysis

Statistical analysis was performed using SPSS statistics for Windows version 23.0 (IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp). Normally distributed continuous variables were presented as mean (standard deviation), while non-normally distributed or continuous non-normally distributed variables were expressed as median (minimum: maximum). Categorical variables were displayed as percentages (%). The normality of data was evaluated using the Kolmogorov-Smirnov test. Non-normally distributed variables were compared using the Mann-Whitney U or Kruskal-Wallis test, while those that were normally distributed were assessed using the Student's t-test or ANOVA. Categorical variable comparisons were conducted using the chi-square or Fisher's exact test. Logistic regression analysis was employed to identify risk factors. A *P*-value of <0.05 was considered statistically significant.

Results

A total of 391 patients were included in the analysis. The mean age was 50.9 (7.7) years, ranging from 36 to 88 years.

The mean BMI was 27.8 (3.6), with values spanning from 17.9 to 38.8 kg/m^2. Among the participants, 241 (61.6%) were premenopausal, while 150 (38.4%) were postmenopausal. The histopathological examination revealed that 349 (89.3%) had benign results, while 42 (10.7%) were classified as having premalignant or malignant conditions. The distribution of histopathological results among the patients is presented in Table 1.

Table 1: Histopathology results of the patients.

	n (%)
Secretory/proliferative endometrium	174 (44.5)
Atrophic endometrium/metaplasia/endometritis	66 (16.8)
Benign endometrial fragments	14 (3.5)
Endometrial polyp	95 (24.2)
Endometrial hyperplasia (atypical /non-atypical)	22 (5.6)
Endometrial intraepithelial neoplasia	13 (3.3)
Endometrial cancer	7 (1.7)

Upon analyzing the patients' clinical and demographic characteristics, it was observed that the mean age in the benign group was significantly lower than that in the malignant group (50.30 [7.16] vs. 55.83 [10.55], *P*<0.001). Furthermore, the proportion of patients over age 60 years was notably higher in the malignant group (Table 2). The groups also exhibited dissimilarities in terms of BMI, with a majority of patients in the malignant group having a BMI >25 kg/m2 (Table 2). Regarding gravidity, parity, systemic diseases, and smoking habits, no substantial differences were noted between the two groups. Notably, the proportion of menopausal patients was significantly higher in the malignant group, and a higher frequency of postmenopausal bleeding complaints was observed within this group (35.5% vs. 61.9%, *P*<0.001). Among premenopausal patients, there were no significant variations in bleeding patterns between the two groups (Table 2).

Table 2: Clinicodemographic characteristics of patients according to groups.

	Benign group (n=349)	Premalignant/ malignant group (n=42)	*P*-value
Age, years	50.30 (7.16)	55.83 (10.55)	<0.001
Age groups, n (%)			
<45 years	82 (23.5)	5 (11.9)	0.002*
45-60 years	240 (68.8)	27 (64.3)	
>60 years	27 (7.7)	10 (23.8)	
BMI, kg/m^2	27.73 (3.67)	29.17 (3.40)	0.018
BMI groups, n (%)			
<25 kg/m^2	76 (21.8)	3 (7.1)	0.007*
25-30 kg/m^2	186 (53.3)	20 (47.6)	
>30 kg/m^2	87 (24.9)	19 (45.2)	
Gravida	2 (0-12)	3 (0-8)	0.445
Parity	2 (0-9)	2 (0-7)	0.599
Any systemic disease, n (%)			
Yes	23 (6.6)	5 (11.9)	0.207*
No	326 (93.4)	37 (88.1)	
Smoking, n (%)	159 (45.6)	20 (47.6)	0.968*
Menopause, n (%)			
No	225 (64.5)	16 (38.1)	0.001*
Yes	124 (35.5)	26 (61.9)	
Premenopausal bleeding pattern, n (%)			
Intermenstrual	72 (31.9)	4 (25.0)	0.601*
Irregular	117 (51.8)	8 (50.0)	
Heavy bleeding	26 (11.5)	2 (12.5)	
Other	11 (4.9)	2 (12.5)	
Postmenopausal bleeding, n (%)	124 (35.5)	26 (61.9)	0.001*
Endometrial thickness, mm	9.41 (2.98)	12.09 (3.59)	<0.001
Premenopausal	10.56 (2.56)	12.56 (3.16)	0.011
Postmenopausal	7.32 (2.52)	11.80 (3.86)	<0.001

BMI: body mass index. Values are given mean (SD) and median (min-max). Mann Whitney-U test was performed. *Chi square test was performed.

In assessing ET through TVUS during the patients' initial presentation, it was evident that the mean thickness was significantly greater in the malignant group compared to the benign group, for both premenopausal and postmenopausal patients (Table 2).

In the logistic regression model applied to identify factors influencing the risk of premalignant/malignant histopathological outcomes, age, the presence of menopause, and ET were found to be significant independent factors (Table 3).

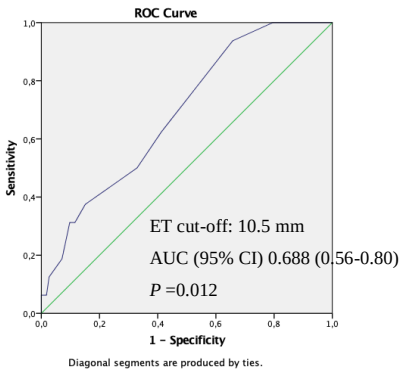
Table 3: Logistic regression analysis for independent factors on premalign/malign histopathology results.

	B	OR (95% CI)	*P*-value
Age, years	0.055	1.05 (1.00-1.11)	0.045
BMI, kg/m^2	0.067	1.06 (0.96-1.18)	0.200
Parity	0.176	1.19 (0.93-1.51)	0.149
Presence of menopause	1.351	3.86 (1.33-11.20)	0.013
ET, mm	0.345	1.41 (1.25-1.59)	<0.001

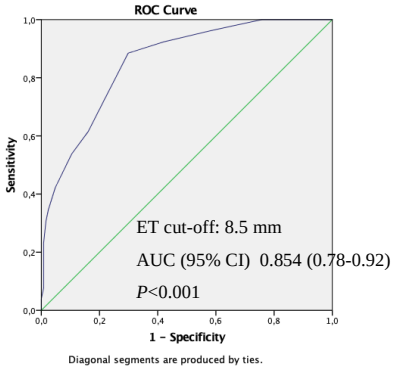
R^2 =0.293, *P*<0.001, BMI: Body mass index, ET: Endometrial thickness

When conducting ROC analysis to determine the optimal ET threshold for malignancy in both premenopausal and postmenopausal patients, the calculated cut-off value for ET was 10.5 mm for premenopausal patients and 8.5 mm for postmenopausal patients (*P*=0.012 and *P*<0.001, respectively) (Figure 1A-B). In premenopausal patients, a threshold of 10.5 mm yielded a sensitivity of 62.5% and a specificity of 58.7% in predicting malignancy (Figure 1A). In postmenopausal patients, a threshold of 8.5 mm demonstrated a sensitivity of 88.5% and a specificity of 70.2% in predicting malignancy (Figure 1B).

Figure 1: ROC analysis for determining the thresholds of endometrial thicknesses for malignancy in premenopausal and postmenopausal patients.



A: ROC analysis for premenopausal patients. The threshold for endometrial thickness (ET) was 10.5 mm with a sensitivity of 62.5%, specificity of 58.7%. AUC: Area under curve, CI: Confidence interval



B: ROC analysis for postmenopausal patients. The threshold for endometrial thickness (ET) was 8.5 mm with a sensitivity of 88.5%, and a specificity of 70.2%. AUC: Area under curve, CI: Confidence interval

Discussion

In individuals with AUB, we conducted a retrospective investigation to identify risk factors associated with the presence of endometrial premalignant and malignant lesions based on patients' demographic information and clinical findings. We found that patients with benign histopathology results tended to be younger and have a lower BMI. Notably, individuals aged 45 years and older with a BMI exceeding 25 kg/m^2 showed a higher frequency of reported premalignant/malignant outcomes.

Regression analysis further confirmed that age, menopause status, and ET were significant predictors for premalignant/malignant endometrial lesions. Upon segmenting patients based on menopause status and examining them in terms of ET, we calculated the ET threshold for premalignant/malignant lesions as 8.5 mm specifically for the postmenopausal group.

Various etiologies contribute to AUB in women during their reproductive years, classified under the FIGO acronym PALM-COEIN [8]. In women with AUB complaints, when suspicion arises following clinical evaluation, endometrial sampling is performed to exclude malignancy. In these cases, age can be considered an important variable in the decision to proceed with biopsy. While there is no globally defined age limit for endometrial biopsy, different guidelines provide divergent recommendations. For instance, Canadian guidelines suggest performing endometrial biopsy in women over the age of 40, whereas the American College of Obstetrics and Gynecology (ACOG) sets the age cut-off at 45 [9,10]. Conversely, studies have reported a lack of correlation between age and endometrial cancer (EC) during the premenopausal period [11]. In our study, we found an increased prevalence of premalignant/malignant endometrial lesions in the presence of AUB among women aged 45 and above, highlighting age as an independent variable for malignancy.

Among the risk factors for endometrial hyperplasia (EH) and endometrial carcinoma, chronic exposure to high estrogen levels or activity was recognized [12]. Obese patients experienced elevated endogenous estrogen levels due to the conversion of androstenedione to estrone and the aromatization of androgens to estradiol, processes occurring primarily in peripheral adipose tissue [13]. In a retrospective study encompassing approximately 900 premenopausal patients with AUB, Wise et al. [11] found that patients with a BMI ≥30 kg/m2 were four times more likely to develop endometrial hyperplasia or carcinoma compared to others. In the current study, although we observed that the majority of patients in the premalignant/malignant group had a BMI above 25, we could not establish this as a significant risk factor. This could be attributed to the smaller number of premenopausal patients in the premalignant/malignant group in our study compared to the study by Wise et al. [11] (16 vs. 41), potentially influencing the statistical power.

Assessment of AUB often begins with imaging methods to identify structural causes, with TVUS being the most commonly utilized technique [14]. Additionally, TVUS is used to assess ET. However, in premenopausal patients, ET can vary due to menstrual cycle fluctuations, limiting its utility in evaluating the presence of endometrial neoplasia. Moreover, consensus is lacking on the cut-off value for ET to detect any abnormality. Furthermore, there are no established screening guidelines for endometrial pathology in premenopausal women with AUB.

Nonetheless, a retrospective study involving premenopausal patients (n=1,084) reported a strong association between ET >13 mm and EH/EC [15]. Our study calculated a premenopausal ET threshold of 10.5 mm with approximately 60% sensitivity and specificity, suggesting its potential association with malignancy. Heremans et al. [16] reported a mean ET of 12.5 mm (95% CI: 10.4-14.6) in the premenopausal group with identified premalignant/malignant conditions and noted that this value could be even thinner in the presence of AUB complaints.

In the case of postmenopausal patients, TVUS can be helpful for endometrial assessment regarding the presence of premalignant/malignant lesions. According to a meta-analysis of around 6,000 postmenopausal patients from 35 prospective studies, when TVUS indicated an ET <5 mm, the probability of endometrial carcinoma was 1% [17]. However, subsequent meta-analyses have suggested that in symptomatic postmenopausal patients, further invasive diagnostic testing should be considered for all patients with a "thin" endometrial thickness [18,19]. A study that included asymptomatic postmenopausal women, reported an ET cut-off value of 6.75 mm with a sensitivity of 84.3% and a specificity of 89.9% for detecting malignancy [20]. In our study, all postmenopausal patients were symptomatic, and we calculated the cut-off value as 8.5 mm. We found that the presence of menopause was a significant determinant for endometrial premalignant/malignant lesions.

In our study focusing on risk factors and management strategies for endometrial premalignant/malignant lesions in women with AUB, several strengths deserve attention. These include the evaluation of each patient by a single physician, consistent application of biopsies and TVUS by the same clinician, inclusion of both premenopausal and postmenopausal patient groups, and the meticulous exclusion of other malignancies and adnexal masses.

Limitations

However, this study has certain limitations that should be acknowledge. The single-center nature, retrospective data collection, absence of additional interventions for advanced endometrial evaluation, inclusion of only symptomatic patients, and the lack of histopathological data from patients who had undergone hysterectomy should be noted as limitations. Future prospective studies could be structured by assessing the data of each patient presenting with AUB, taking into account their hysterectomy outcomes.

Conclusion

In conclusion, our study underscores the significance of a personalized approach in managing patients with AUB, considering essential factors such as age, BMI, ET, and menopausal status. This approach offers a valuable means to circumvent unnecessary interventions and ensures that high-risk patients are directed toward specialized assessment when warranted. However, to refine our understanding and establish well-defined risk factor thresholds, the need for multicenter, high-volume prospective studies becomes evident. By embracing this pursuit, we can pave the way for more precise clinical guidelines and improved patient care in the realm of abnormal uterine bleeding.

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