




Original Research

Factors Associated with Abnormal Uterine Bleeding in Perimenopausal Women

Radenko Ivanović^{1,2}, Bojan Joksimović², Vladimir Čančar^{1,2}, Helena Marić^{2,3},
Draženka Matović⁴, Nenad Lalović^{2,3}, Radiša Pavlović⁵, Miloš Milosavljević^{6,*},
Jovana Milosavljević⁷, Slobodan Janković⁶

¹Department of Gynecology and Obstetrics, University Hospital Foča, 73300 Foca, Republic of Srpska, Bosnia and Herzegovina

²Faculty of Medicine in Foča, University of East Sarajevo, 73300 Foca, Republic of Srpska, Bosnia and Herzegovina

³Department of Surgery, University Hospital Foča, 73300 Foca, Republic of Srpska, Bosnia and Herzegovina

⁴Department of Anesthesiology and Reanimation, University Hospital Foča, 73300 Foca, Republic of Srpska, Bosnia and Herzegovina

⁵Department of Pharmacy, Faculty of Medical Sciences, University of Kragujevac, 34000 Kragujevac, Serbia

⁶Department of Pharmacology and Toxicology, Faculty of Medical Sciences, University of Kragujevac, 34000 Kragujevac, Serbia

⁷Department of Anatomy, Faculty of Medical Sciences, University of Kragujevac, 34000 Kragujevac, Serbia

*Correspondence: milosavljevicmilos91@gmail.com (Miloš Milosavljević)

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Abstract

Background: Abnormal uterine bleeding (AUB) is one of the most common health problems encountered in women of the perimenopausal age group. The aim of this study was to investigate the characteristics of functional AUB in perimenopausal women, and to identify predictors of the occurrence of functional AUB in perimenopausal women. **Methods:** This was a cross-sectional study that included 45 women with complaints of AUB admitted to the gynecology ward in the University Hospital in Foča, and 45 women without AUB who underwent a gynecological examination in the Primary Health Center in Foča, Bosnia and Herzegovina. We included women with AUB who had a normal ultrasound finding without obvious genital or cervical lesions, and who were not on hormonal therapy. The existence of AUB was determined on the basis of a clinical examination by a gynecologist and existing medical documentation. A logistic regression model was used to assess the possible relationship between the occurrence of the functional AUB and the risk factors for its occurrence. **Results:** The mean patient age was 48.38 ± 2.40 years. There was no significant difference in age, frequency of physical activity, or previous use of oral contraceptives between the two groups of patients divided by the presence of the functional AUB in perimenopause. The logistic regression model showed that age ($p = 0.008$), high values of body mass index (BMI) ($p = 0.001$), consumption of alcohol and cigarettes on a daily basis ($p = 0.001$), and hypertension ($p = 0.046$) represented significant risk factors associated with functional AUB in perimenopausal women. **Conclusions:** During routine exams of women approaching menopause, gynecologists should emphasize the harms of smoking and alcohol use, as well as the significance of non-pharmacological and pharmacological methods for the treatment of obesity and hypertension.

Keywords: abnormal uterine bleeding; perimenopause; menopause; risk factors

1. Introduction

Abnormal uterine bleeding (AUB) is a common gynecological disorder, and it is the main reason for the consultation of a gynecologist in a primary care setting [1]. AUB is defined as a symptom, not a disease, that occurs in different abnormal patterns, but the common feature of AUB is that it does not correspond with the duration, frequency, and amount of blood in a normal menstrual cycle [2]. It occurs in various forms, such as heavy menstrual bleeding or intermenstrual bleeding. Furthermore, it may result from causes such as anovulation, uterine pathology, pregnancy, and coagulopathies [3]. AUB accounts for up to 20% of office visits prior to perimenopause [4], while in perimenopausal and postmenopausal age, this condition accounts for up to 70% of new gynecological consultations [1].

Perimenopause, or menopause transition, is defined as the period prior to menopause when a woman may experience irregular or variable menstrual cycles and fluctuations in reproductive hormones, and may last up to 2 to 8 years [5,6]. The median age of perimenopause is 47.5 years, and 87% of women are perimenopausal or postmenopausal by the age of 51 [7]. Perimenopause can be associated with a wide spectrum of disorders, and AUB is one of the most common health problems encountered in women of the perimenopausal age group [8]. As a result of hormonal changes in the hypothalamic-pituitary-ovarian axis, ovulations are irregular during perimenopause. In early perimenopause, inhibin B levels decrease, which results in a rise in the follicle-stimulating hormone (FSH). The rise of FSH is periodic, and it may rise during some cycles and return to premenopausal levels in subsequent cycles. Similarly, concen-



trations of estradiol may also rise or even decline in perimenopausal women, which is predominantly a consequence of the decline in ovarian follicle numbers [9–11].

It has been proposed that an increase in menstrual blood loss in perimenopausal women is likely to be a result of ovulatory cycles, which are followed by prolonged periods of anovulation with elevated concentrations of estradiol. This contributes to abnormal proliferative changes in the endometrium and variable ovulatory cycle length. However, the etiology and pathogenesis of AUB in perimenopausal women are not yet completely known and understood [12]. Rarely, the cause of AUB in perimenopausal women could be the clinical presentation of benign or malignant lesions of the female reproductive organs [13]. However, there are only a few studies that have evaluated the risk factors related to AUB in perimenopausal women.

Therefore, the aim of our study was to investigate the characteristics of functional AUB in perimenopausal women and to identify predictors for the occurrence of functional AUB in perimenopausal women.

2. Material and Method

This was a cross-sectional study from April 2019 to October 2019, consisting of 90 patients in the perimenopausal age group (45 to 53 years of age). This study included 45 women with complaints of AUB admitted to the gynecology ward of the University Hospital in Foča, Bosnia and Herzegovina, and 45 women without AUB who underwent a gynecological examination at the gynecological department of the Primary Health Center in Foča, Republic of Srpska, Bosnia and Herzegovina. The Ethics Committee of the University Hospital in Foča had approved the study prior to its initiation (No 1/17).

We included women with functional AUB (FIGO (International Federation of Gynecology and Obstetrics)-COEIN AUB) whose potential causes belong to the groups of coagulopathies (C), ovulatory dysfunctions (O), endometrial disorders (E), iatrogenic (I), and not classified (N) disorders [14]. Those patients had normal ultrasound finding without obvious genital or cervical lesions and were not on hormonal therapy. The exclusion criteria were structural causes of AUB: polyps (P), adenomyosis (A), leiomyoma (L), malignancy, and hyperplasia (M) (FIGO-PALM AUB) [14]. Furthermore, we excluded women who had uterine and ovarian abnormalities that were confirmed by ultrasonography. Pregnant women, women on oral contraceptives, patients who did not want to participate in the trial, patients with premalignant and malignant cervix lesions, and patients who needed therapeutic curettage owing to severe bleeding were also excluded.

The following data were collected from the medical files of women included in the study: age, place of living (urban or rural area), educational level, smoking, consumption of alcohol, physical activity, body weight, presence of chronic diseases (hypertension, diabetes mellitus, others),

the use of hormonal contraceptives in the last 10 years, data for other medications used by the participants (antihypertensives, drugs for the treatment of angina pectoris and heart failure, antidiabetic drugs, thrombosis prevention drugs), data for previous genital surgeries, previous inflammatory diseases of the genital organs, number of births, and number of miscarriages.

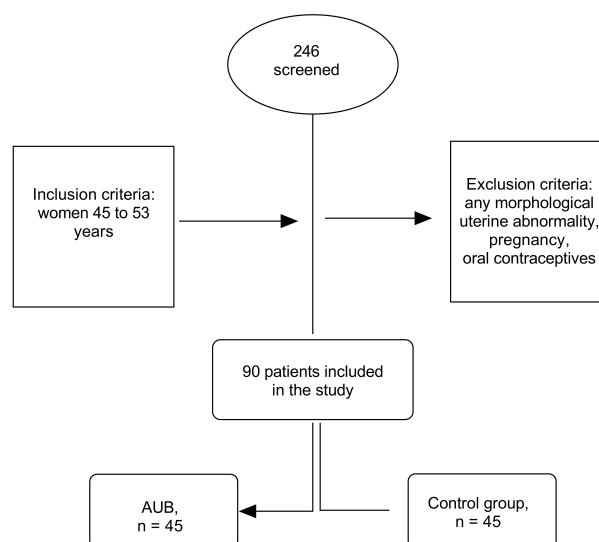


Fig. 1. Flowchart with a detailed description of the study population. AUB, abnormal uterine bleeding.

Laboratory blood analysis was performed in the biochemical laboratory at the University Hospital in Foča. Hormonal status is defined by the values of FSH, luteinizing hormone (LH), prolactin, estradiol, progesterone, and testosterone. Hormone concentrations were determined by the radioimmunoassay (RIA) method, using Cisbio (CIS) biointernational kit (Branch of/Subsidiary of Schering SA, Saint-Aubin, France) for determination of FSH, LH, prolactin, estradiol, progesterone, and testosterone, according to manufacturer instructions. Reference values for hormones are given by the appropriate method.

Based on a gynecological clinical examination and previous medical records, it was determined whether dysfunctional perimenopausal bleeding existed. The existence of AUB was determined through the assessment of hemodynamic instability and anemia, the exclusion of morphological causes of bleeding, and the exclusion of pregnancy [15]. The AUB group thus included patients whose bleeding fell beyond the population-based 5th to 95th percentiles, adjusted for monthly regularity, volume, duration, and frequency [16]. Transvaginal ultrasonography (Voluson E8, General Electric, Boston, MA, USA) was performed on every patient, and it also served as a criterion for the inclusion of patients in the study [15].

Table 1. Differences in age, physical activity, BMI, alcohol and cigarette consumption, previous use of contraceptive, and number of births between perimenopausal women with and without AUB.

Variables	AUB		CG		Total		$p\left(\chi^2\right)$
	(n = 45)		(n = 45)		(n = 90)		
	n	%	n	%	n	%	
Age							
42 to 48 years	22	48.9	15	33.3	37	41.1	0.134
49 do 53 years	23	51.1	30	66.7	53	58.9	
Physical activity							
Inactive	12	26.7	18	40.0	30	33.3	0.281
Relitevely active	21	46.7	20	44.4	41	45.6	
Active	12	26.7	7	15.6	19	21.1	
BMI (kg/m ²)							
≤24.9	8	17.8	24	53.3	32	35.6	<0.001*
≥25	37	82.2	21	46.7	58	64.4	
Use of alcohol and cigarettes							
Yes	37	82.2	21	46.7	58	64.4	<0.001*
No	8	17.8	24	53.3	32	35.6	
Use of oral contraceptives							
Yes	13	28.9	16	35.6	29	32.2	0.499
No	32	71.1	29	64.4	61	67.8	
Number of births							
One	6	13.3	13	28.9	19	21.1	0.029*
Two	26	57.8	16	35.6	42	46.7	
Three or more	13	28.9	16	35.6	29	32.2	

AUB, group of patients with abnormal uterine bleeding; CG, control group (group of perimenopausal women without AUB); BMI, body mass index; χ^2 , Chi-square test;

*statistically significant ($p < 0.05$).

The calculation for the minimal sample size was made using G Power software (version: 3.1.9.4, G*Power, Dusseldorf, Germany) using a Chi-square test for a defined study power of 80% and a probability of first-type statistical error of 5%. The independent variable “presence of comorbidities” was used for calculating the minimum sample size. According to Rezende *et al.*'s [17] study, comorbidities were present in 39.0% of women with AUB, as opposed to 12.0% of women in the control group. Using these parameters, a total sample size of 37 patients per group, or a minimum of 74 patients, was calculated.

The data were analyzed using descriptive and analytical statistical methods. Means and standard deviations (SD) were used for presenting continuous data and frequencies (percentages) for presenting categorical variables. The chi-square and Mann-Whitney U tests were used to compare differences between groups. A logistic regression model was used to assess the possible relationship between the occurrence of AUB and the risk factors for its occurrence. All statistical analyses were performed using IBM SPSS Statistics Software version 18.0 for Windows (IBM Corp., Armonk, NY, USA). All p values lower than 0.05 were considered statistically significant.

3. Results

In total, we included 90 patients in our study, 45 with AUB and 45 in the control group. A detailed description of the study population, including reasons for the exclusion of participants is shown in Fig. 1.

The mean patient age was 48.38 ± 2.40 years. There was no significant difference in age, frequency of physical activity, or previous use of oral contraceptives between the two groups of patients. However, patients with functional AUB had a significantly higher body mass index (BMI) (82.2%) in comparison to the control group (46.7%) ($p < 0.001$). Also, patients with functional AUB significantly consumed alcohol and cigarettes more often when compared to the control group of patients (82.2% vs. 46.7%, $p < 0.001$). Moreover, women with three or more births significantly less frequently had functional AUB (28.9%) when compared to the control group (35.6%) ($p = 0.029$) (Table 1).

Most patients (84.4%) did not have diabetes mellitus, while 28.9% of women had hypertension. There was no difference between groups in the frequency of diabetes mellitus (22.2 vs. 8.9, $p = 0.081$), but hypertension was significantly more prevalent in the AUB group (40.0%) when compared to the control group of patients (17.8%) ($p =$

Table 2. Frequency of comorbidities such as diabetes mellitus and hypertension, and use of therapy for comorbidities among perimenopausal women with and without AUB.

Variables	AUB		CG		Total		$p\ (\chi^2)$
	(n = 45)		(n = 45)		(n = 90)		
	n	%	n	%	n	%	
Diabetes mellitus							
Yes	10	22.2	4	8.9	14	15.6	0.081
No	35	77.8	41	91.1	76	84.4	
Hypertension							
Yes	18	40.0	8	17.8	26	28.9	0.020
No	27	60.0	37	82.2	64	71.1	
Use of therapy for comorbidities							
Yes	40	88.9	21	46.7	61	67.8	<0.001*
No	5	11.1	24	53.3	29	32.2	

AUB, group of patients with abnormal uterine bleeding; CG, control group (group of perimenopausal women without AUB); χ^2 , Chi-square test; *statistically significant ($p < 0.05$).

0.020). Furthermore, patients from the AUB group (88.9%) used therapy for chronic conditions more often in comparison to the control group (46.7%) ($p < 0.001$) (Table 2).

Next, Fig. 2 shows ultrasound measurements of the uterus (A), and ovary (B, C) among perimenopausal women with and without AUB. Statistical analyses showed that between the two groups of patients, there was no statistical significance in uterine length (Fig. 2A, left). However, mean values of uterine width (44.44 ± 3.81 mm) and height (36.57 ± 4.93 mm) were significantly higher in the AUB group of patients when compared to the control group (width: 42.13 ± 3.01 mm, $p = 0.020$) (height: 32.08 ± 3.61 mm, $p < 0.001$) (Fig. 2A). The mean values of the length (29.35 ± 3.30 mm), width (21.31 ± 2.40 mm) and height (14.60 ± 1.85 mm) of the right ovaries were significantly lower in the AUB group when compared to the control group (31.31 ± 1.23 mm; 24.75 ± 1.77 mm; 17.24 ± 2.49 mm) ($p < 0.001$) (Fig. 2B). Similarly, mean values of the length (28.33 ± 3.00 mm), width (20.20 ± 2.64 mm) and height (13.60 ± 2.01 mm) of the left ovaries were significantly lower in the AUB group when compared to the control group (30.35 ± 1.92 mm; 24.66 ± 2.92 mm; 16.20 ± 3.85 mm) ($p < 0.001$) (Fig. 2C). The mean values of endometrial thickness measured by ultrasound were significantly higher in the AUB group of patients (13.24 ± 2.00 mm) in comparison to the control group (11.00 ± 2.19 mm) ($p < 0.001$) (Fig. 3).

Next, serum levels of reproductive hormones in perimenopausal women with and without functional AUB were evaluated (Fig. 4). Patients with functional AUB had significantly higher mean values of FSH (33.88 ± 13.93 mIU/mL), estradiol (115.12 ± 148.56 pg/mL) and prolactin (17.38 ± 12.98 mIU/mL) in comparison to the control group (12.33 ± 11.81 mIU/mL; 36.47 ± 14.39 pg/mL; 15.28 ± 49.89 mIU/mL) ($p < 0.001$). On the other hand, the levels of progesterone (0.33 ± 0.17 ng/mL) and testosterone

(0.50 ± 0.46 nmol/L) were significantly lower in comparison to the control group (0.43 ± 0.14 ng/mL, $p < 0.001$; 0.56 ± 0.28 nmol/L, $p < 0.010$). However, differences in mean values of LH between those two groups of patients were not observed (Fig. 4).

The results of both univariate and multivariate stepwise backward conditional binary logistic regression from the last step with satisfactory goodness of fit (Cox & Snell R square 0.396, Nagelkerke R² 0.527) with adjustment for potential confounders are shown in Table 3. After adjustment for potential confounders and other independent variables, it was shown that age, high values of BMI, consumption of alcohol and cigarettes on a daily basis, and the use of therapy for chronic comorbidities, all represent significant risk factors associated with functional AUB in perimenopausal women.

4. Discussion

This study showed that age, high BMI, alcohol and cigarette consumption, and the use of therapy for chronic comorbidities may be associated with the occurrence of functional AUB in perimenopausal women. It is critical to recognize and address all variables that contribute to the development of AUB since it involves severe menstrual and intermenstrual bleeding, which can result in anemia, or be misdiagnosed as cancer.

The older age of the participants in our study was shown to be a risk factor for the onset of AUB. Literature data on age as a potential predictor for AUB is scarce. However, in a study conducted on 200 patients aged 40–55 years, patients were divided by age into three groups: 40–45, 45–50, and over 50 years. The highest prevalence of AUB (66%) was recorded in the population between 45 and 50 years of age [18]. An almost identical prevalence

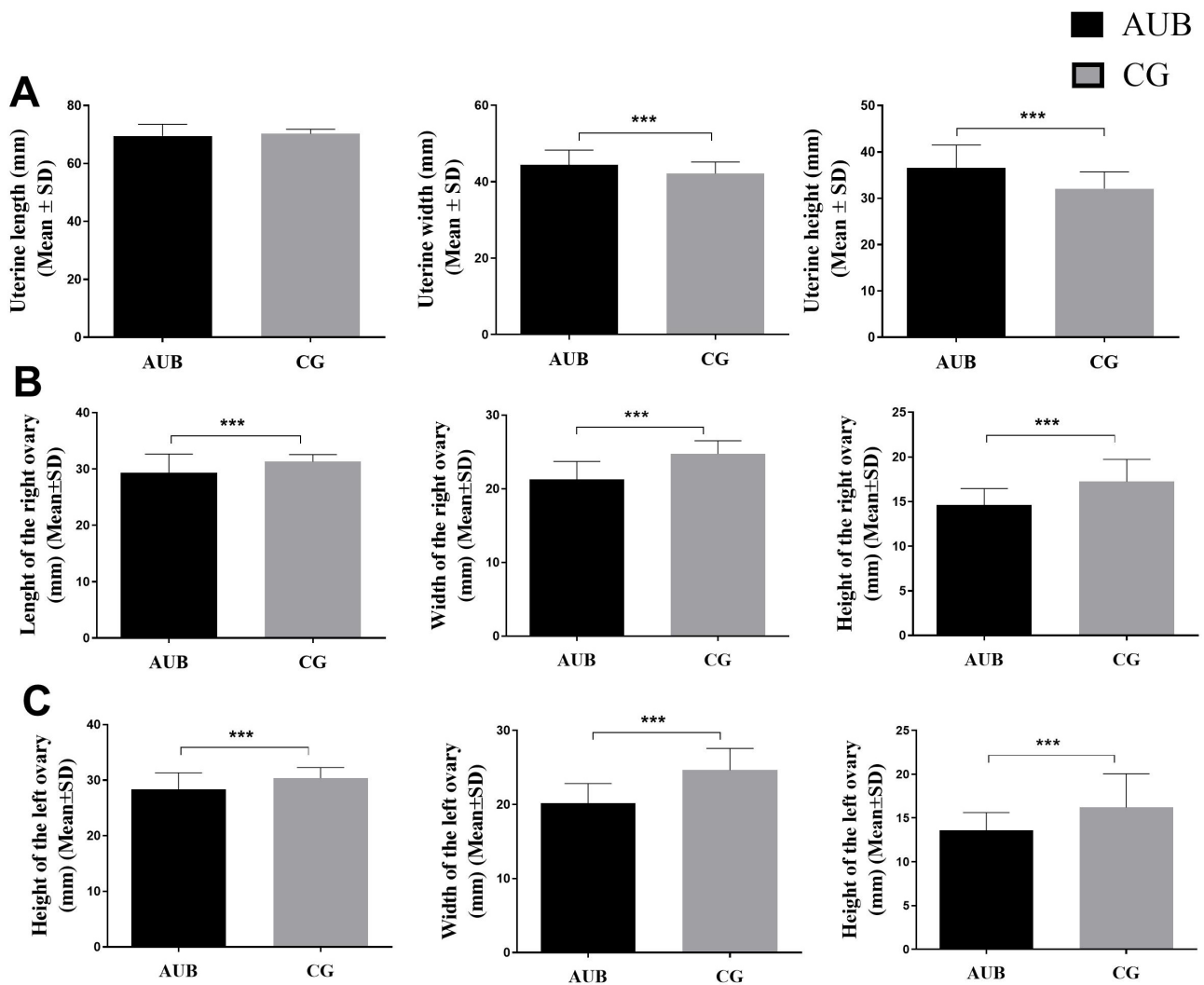


Fig. 2. Ultrasonographic (US) measures of uterus, right and left ovary among perimenopausal women with and without AUB. (A) US measures of uterus, (B) US measures of right ovary, (C) US measures of the left ovary. Mean \pm standard deviation (SD) (mm); Mann-Whitney U test (***) $p < 0.001$. AUB, group of patients with abnormal uterine bleeding; CG, control group (group of perimenopausal women without AUB).

(65.55%) of AUB in the same age group (45–50) was found in another observational study, with the non-organic cause being the most common [8].

Increased body weight and changes in fat deposition are frequent in the menopausal transition period. Women in this period are at a higher risk of losing lean body mass and experiencing unfavorable fat redistribution, which may contribute to the development of metabolic disorders, including central obesity. The risk of developing obesity increases significantly in the perimenopausal period [19]. In a study that investigated the influence of BMI (among other predictors) on heavy menstrual bleeding (among other outcomes) in a population of more than 17,000 cases and almost 240,000 controls, aged from 40 to 69, the authors showed that increased BMI is a risk factor for AUB based on both observational and genetically predicted associa-

tion [20]. The possible mechanism may be related to the fact that increased BMI has an impact on endometrial function, and thus the development of AUB. In perimenopausal women, and to a greater extent in postmenopausal women with a high BMI, low or no progesterone and leptin resistance can reduce endometrial proliferation, delay its repair, and produce AUB. In addition, women with AUB have an increased endometrial inflammatory response, suggesting tumor necrosis factor (TNF) as the main factor involved in the etiology of AUB [21].

Our results showed the strongest association between alcohol and cigarette consumption and AUB (odds ratio (OR) = 4.182). It is well known that both alcohol and cigarette consumption may lead to various pathological conditions. In a database study investigating the risk factors for bleeding irregularity among 4788 women, current

Table 3. Risk factors for AUB in perimenopausal women.

Variables	Univariate	Multivariate	Multivariate
	<i>p</i> -value*	<i>p</i> -value	Exp (B) with 95% confidence interval
Age	0.017*	0.005*	1.535 (1.135–2.076)
High values of BMI	0.001*	0.003*	6.138 (1.868–20.170)
Alcohol and cigarettes consumption	0.001*	0.022*	4.182 (1.229–14.233)
Previous use of oral contraceptives	0.499	0.348	2.104 (0.446–9.936)
Number of births	1.000	0.404	1.382 (0.646–2.957)
Number of miscarriages	0.083	0.248	0.771 (0.497–1.198)
Diabetes mellitus	0.091	0.106	3.743 (0.756–18.537)
Hypertension	0.023*	0.424	1.821 (0.419–7.921)
Use of therapy for chronic comorbidities	0.000*	0.001*	10.491 (2.707–40.660)

*statistically significant ($p < 0.05$).

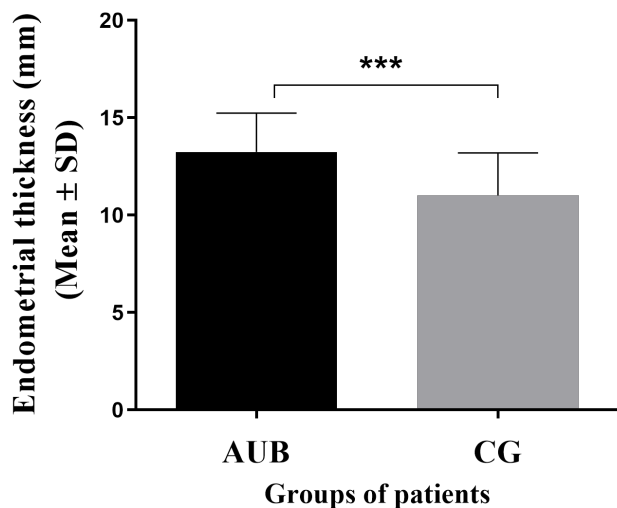


Fig. 3. Endometrial thickness measured by US among perimenopausal women with and without AUB. Mean \pm standard deviation (SD); Mann-Whitney U test ($***p < 0.001$). AUB, group of patients with abnormal uterine bleeding; CG, control group (group of perimenopausal women without AUB).

smokers had a 1.4 times higher risk of developing irregular uterine bleeding [22]. Similarly, smoking status was a significant risk factor for AUB onset, showing an almost identical association ($OR = 1.42$) [23]. In addition to AUB onset, smoking is also a significant risk factor for early menopause onset due to the low estrogen, diminished ovarian reserve, and shorter perimenopausal period. Altogether, these findings suggest the possibility that the AUB group

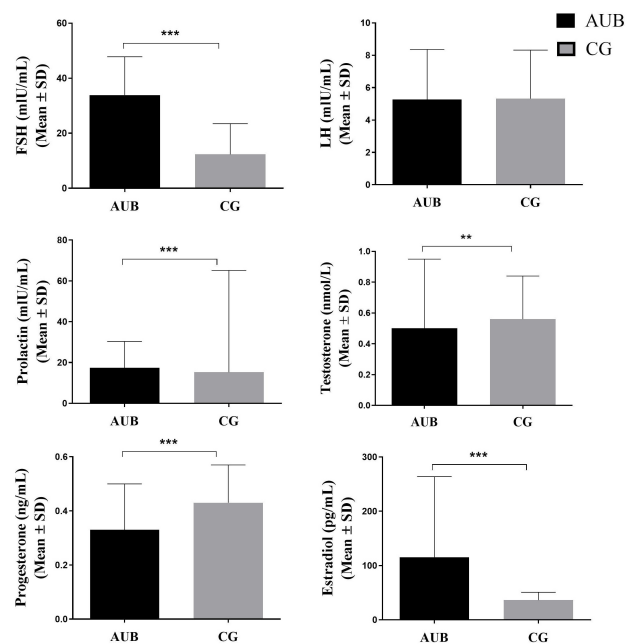


Fig. 4. Serum hormones profiles in perimenopausal women with and without AUB. Mean \pm standard deviation (SD); Mann-Whitney U test ($**p < 0.010$; $***p < 0.001$). AUB, group of patients with abnormal uterine bleeding; CG, control group (group of perimenopausal women without AUB); FSH, follicle-stimulating hormone; LH, luteinizing hormone.

in the present study entered the perimenopausal period earlier. Contrary, alcohol consumption may increase estrogen levels and thus delay menopausal onset [24]. That is the

possible reason for the lack of association between alcohol consumption and AUB in previous reports, which analyzed the influence of alcohol alone [22,23]. It has been previously suggested that alcohol consumption might increase the prevalence of obesity, and consequently affect the onset of AUB. However, it may be plausible and more cautious to consider the integration of modifiable risk factors such as smoking, obesity, and alcohol consumption, given their interdependence [22]. As such, we assessed the potential predictor value of alcohol consumption concomitant with cigarette smoking. Indeed, their interdependence resulted in a 4.182 higher risk for AUB onset in the group of patients concomitantly consuming cigarettes and alcohol, suggesting that smoking might be an even stronger risk factor than drinking alcohol alone, which is in accordance with previous results [23].

A high-risk profile for a AUB patient is an obese woman of advanced age, with a number of comorbidities, who smokes and drinks alcohol, at least occasionally. Such a profile should alert any practicing gynecologist to inquire about AUB and to advise the patient to make an effort to control their habits or to seek proper treatment for existing comorbidities.

The limitations of our study include its monocentric nature, the possibility of inaccurate or incomplete information from the medical files of patients, and the relatively small sample size and heterogeneity of the research population, which can be a significant source of bias. These limitations can lead to the omission of some important risk factors that contribute to the occurrence of functional AUB, but also to an overestimation of the influence of some factors with an objectively weaker influence on the occurrence of this disorder. Also, in our cross-sectional study, the patients were not followed up after the first contact with the investigators, and the investigators were not involved in diagnostic procedures performed. Therefore, the results of additional diagnostics remained unknown.

5. Conclusions

In conclusion, we could say that age, obesity, consumption of alcohol and cigarettes, and the use of therapy for chronic comorbidities are significant predictors of the occurrence of functional AUB in perimenopausal women. During routine exams of women approaching menopause, gynecologists should emphasize the harms of smoking and alcohol use, as well as the significance of non-pharmacological and pharmacological methods for the treatment of obesity and hypertension.

Availability of Data and Materials

The data that support the findings of this study are available on the request from the corresponding author.

Author Contributions

RI, MM, RP, JM and SJ designed and planned the study. RI, VČ, HM, DM and NL were responsible for data acquisition. RI, SJ, BJ and MM performed statistical data analysis. RI, BJ, RP, MM and JM wrote the manuscript. SJ, VC, HM, DM and NL edited the manuscript. All authors read and approved the final version of the manuscript.

Ethics Approval and Consent to Participate

The Ethics Committee of the University Hospital in Foča had approved the study prior to its initiation (No 1/17). Written informed consent has been obtained from the patients to publish this paper.

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Conflict of Interest

The authors declare no conflict of interest.

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