

ANORMAL UTERİN KANAMALI KADINLARDA ENDOMETRİYAL BİYOPSİ SONUÇLARININ MENOPOZ DURUMUNA GÖRE KARŞILAŞTIRILMASI

COMPARISON OF ENDOMETRIAL BIOPSY RESULTS IN WOMEN WITH ABNORMAL UTERINE BLEEDING ACCORDING TO THE MENOPAUSAL STATUS

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ÖZET

AMAÇ: Anormal uterin kanamalar (AUK) kadınlarda, jinekoloji polikliniğine başvurunun en yaygın nedenlerinden biridir. Bu çalışmada, anormal uterin kanaması olan kadınlarda, kadınların AUK'ü öz değerlendirmeleri ve endometriyal biyopsi sonuçlarını menopoz durumuna göre karşılaştırdık.

GEREÇ VE YÖNTEM: Çalışma, tanımlayıcı, kesitsel olarak tasarlanmış ve AUK'lı 650 kadın ile gerçekleştirilmiştir. Veriler tanımlayıcı bilgi formu ve endometriyal biyopsi sonuçları ile elde edilmiştir.

BULGULAR: Çalışmaya katılan kadınların %29.6'sı menopozda olup, %70.4'ü menopozda değildir. Endometriyal biyopsi sonuçları, %3.4'ünün endometriyal kanser, %7.4'ünün yetersiz materyal ve %11.2'sinin atipik hiperplazi olduğunu gösterdi. Postmenopozal dönemde olan kadınlarda atipik hiperplazi daha yüksek bulundu ($p<0.05$).

SONUÇ: Kadınlarda atipik hiperplazi oranının yaş ve AUK özellikleri ile arttığı belirlendi. Atipik hiperplazi postmenopozal dönemdeki kadınları daha fazla etkilemektedir. Atipik hiperplazili kadınların düzenli ve periyodik takibi malignite riskinin teşhisi için önemlidir. Yetersiz materyal oranının yüksek olması da önemli bir endişe kaynağıdır. Bu prosedürleri uygulayan sağlık uzmanları, doğru teşhisi koyarken dikkatli olmalıdır. Geçtiğimiz yıl boyunca AUK özellikleri yaşayan kadınların hastaneye başvurularını geciktirdikleri belirlenmiştir. Bu nedenle, kadınların AUK hakkında bilgilendirilmesi çok önemlidir.

ANAHTAR KELİMELE: Uterin kanama, Endometriyal kanser, Menopoz.

ABSTRACT

OBJECTIVE: Abnormal uterine bleeding (AUB) is one of the most common reasons for women to present to the gynecology outpatient clinic. In this study, we compared abnormal uterine bleeding self-assessments and endometrial biopsy results in women with AUB according to the menopausal status.

MATERIAL AND METHODS: The study was designed as a descriptive, cross-sectional one and was conducted on 650 women with AUB. Data were obtained by descriptive information form and endometrial biopsy results.

RESULTS: It was determined that 29.6% of the study participants were in the postmenopausal period, while 70.4% were in the non-menopausal period. The endometrial biopsy results demonstrated that 3.4% were endometrial cancers, 7.4% were inadequate material, while 11.2% were atypical hyperplasia. Atypical hyperplasia was found to be higher in women who were in the postmenopausal period ($p < 0.05$).

CONCLUSIONS: It was determined that the rate of atypical hyperplasia in women increased with age and AUB characteristics. Atypical hyperplasia was found to affect a greater number of women in the postmenopausal period. Regular and periodic follow-up of women with atypical hyperplasia is important in determining the risk of malignancy. The high rate of inadequate material is also of significant concern. The healthcare professionals who perform these procedures must be careful in making the correct diagnosis. It has been determined that women who have experienced AUB over the past year, have delayed their admission to the hospital. Therefore, it is crucial to inform women about AUB.

KEYWORDS: Uterine hemorrhage, Endometrial cancer, Menopause.

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INTRODUCTION

Abnormal Uterine Bleeding (AUB) is acute or chronic bleeding that is abnormal in pattern, amount, frequency or duration, originating from the uterus, unrelated to pregnancy. Acute AUB is defined as an episode of heavy bleeding that required intervention according to the clinician, whereas chronic AUB is defined as abnormalities in quantity, pattern, and/or timing that occurred in the majority of the last 6-month cycles. The International Federation of Gynecology and Obstetrics (FIGO) has developed a classification system (PALM-COEIN) for AUB in 2011. PALM-COEIN: Polyp; Adenomyosis; Leiomyoma; Malignancy and hyperplasia; Coagulopathy; Ovulatory dysfunction; Endometrial disorders; Iatrogenic; and Not otherwise classified. In this classification, the PALM group includes structural lesions of the uterus, while COEIN consists of non-structural causes (1). In the 2018 revision of FIGO, a normal menstrual cycle has a frequency of 24 to 38 days and lasts ≤ 8 days. In FIGO 2011, the definition of menstrual irregularity was defined as variations in which the cycle lengths differed more than 20 days in a year; In the revision in 2018, this definition was changed to variations over 7-9 days depending on age. Besides, in the FIGO 2018 revision, instead of the amount of bleeding expressed in milliliters in the previous classification, the patient expression as low, normal, and excessive is preferred based on the amount of bleeding that may affect the quality of life of the woman. Variations in any of these four parameters constitute AUB (2). AUB is one of the most common reasons for admission to the gynecology outpatient clinic (3) and it can be the first sign of the endometrial malignancy (4). The rate of AUB in women with endometrial cancer in the postmenopausal period is more than 90% (5).

Endometrial cancer is the 15th most common cancer worldwide (6). It is also the fourth most common cancer among Turkish women (7).

Evaluation of the endometrial tissue sample is recommended for all women over 45 years of age who have experienced AUB, for the early diagnosis of endometrial cancer (8). Although there are several studies on women with AUB that examine the biopsy results, these studies

are retrospective and do not include how women evaluate AUB based on whether they are in menopause presence (9 - 11). Women experience both, feel shameful in admission for gynecological examination (12) and also believe in myths about AUB (13). For this reason, women may delay the self-evaluation of AUB and, thus hospital admission. Therefore, the association between endometrial biopsy results and AUB assessment of pre and post-menopausal women may be an important indicator of endometrial cancer.

This study thus aimed to compare AUB evaluations and endometrial biopsy results in women with AUB, according to their menopausal status.

MATERIAL AND METHODS

Design and Settings

This cross-sectional, descriptive study was carried out in a gynecological unit where the gynecological interventions were performed in a training and research hospital between 07 May 2018 and 31 August 2018. This unit usually conducts diagnostic procedures and revision of curettage (minor surgical procedures).

On the morning of the day of minor surgery, women are registered to this unit. Then, minor surgical procedure, follow-up and treatment of the patient is performed. The patient is discharged on the same day (if no complications are found). The average number of visitors a month is 450–500 women. The biopsy is carried out by the physician in this unit, while the nurse prepares the patient for the procedure and cares for the patient during and after the procedure. During the data collection period of the study, biopsy samples were examined by different pathologists working in the hospital.

Samples

The study involved 650 women who visited the gynecological unit between 07 May and 31 August 2018 and met the sampling criteria. The eligibility criteria included women with 1) complaint of AUB (ongoing since the last year), 2) decision for endometrial biopsy, 3) over 18 years of age, 4) ability to speak and understand Turkish, 5) who have not undergone hormone replacement therapy, and 6) volunteering to

participate in the study. The study was conducted in accordance with the principles of the Declaration of Helsinki. The participation of respondents was voluntary, and informed consent was obtained from each participant before the study.

Data Collection

All participants were evaluated through the Descriptive Information Form. The Descriptive Information Form included demographic information such as age, educational, and employment status, as well as obstetric information, and characteristics of the AUB. Also, endometrial biopsy results were recorded in this form.

Statistical Analysis

All analyses were performed using SPSS, version 22.0. The data were presented as mean \pm SD and percentages. The relationship between categorical variables was tested using chi-square and logistic regression analysis. Statistical significance was accepted when p-value was less than < 0.05 (14).

Ethical Committee

The study was approved by the Non-Intervention Research Assessment Commission of the Izmir Training and Research Hospital (Ethical Consideration Number: 2018/4-4, Date: 25/04/2018).

RESULTS

This study conducted with a total of 650 women, of whom 458 were non-menopausal and 192 were post-menopausal. The mean age of non-menopausal women was 42.8 ± 5.7 , 88.9% were married, 86.5% were educated at primary level or beyond, 65.7% were non-working, and 86.7% belonged to middle-income category. The mean age of post-menopausal women was 56.0 ± 8.2 , 75% were married, 73% received primary education or more, 66.1% were non-working, and 79.7% belonged to the middle-income category (**Table 1**). In the non-menopausal period, 83.6% of women were observed to be using contraceptive methods. The mean duration of contraceptive method use was 9.84 years. The most commonly used contraceptive method was intrauterine device (27.9%). It was determined that 70.3% of women in postme-

nopausal period used a contraceptive method before go through menopause. The mean duration of contraceptive method use was 13.90 years. The most commonly used contraceptive method in this group was intrauterine device (40.7%) (**Table 2**).

Table 1: Descriptive Characteristics (n: 650)

Characteristics	Non-menopausal		Postmenopausal		Total	
Age ($\bar{x} \pm SD$)	42.8 \pm 5.7		56.0 \pm 8.2			
	n	%	n	%	n	%
Age (years)						
Less than 40	150	32.8	3	1.6	153	23.5
40-50	276	60.3	48	25.0	324	49.8
More than 50	32	6.9	141	73.4	173	26.7
Marital Status						
Single	51	11.1	48	25.0	99	15.2
Married	407	88.9	144	75.0	551	84.8
Educational Status						
Illiterate	54	11.8	43	22.4	97	14.9
Literate	8	1.7	9	4.6	17	2.6
Primary school	253	55.2	112	58.3	365	56.2
Secondary school	112	24.5	20	10.5	132	20.3
University	31	6.8	8	4.2	39	6.0
Working Status						
Working	157	34.3	65	33.9	222	34.2
Not working	301	65.7	127	66.1	428	65.8
Economical Status						
Income less than expenses	33	7.2	27	14.1	60	9.2
Income equivalent to expenses	397	86.7	153	79.7	550	84.6
Income is more than expenses	28	6.1	12	6.3	40	6.2
Total	458	70.4	192	29.6	650	100

Table 2: Obstetric and AUB Characteristics (n: 650)

Characteristic	Non-menopausal (n:458)		Postmenopausal (n:192)		Total	
	n	%	n	%	n	%
Use of Contraceptive Methods						
Yes	383	83.6	135	70.3	518	79.7
No	75	16.4	57	29.7	132	20.3
Contraceptive Method Used						
Intrauterine device	107	27.9	55	40.7	162	31.2
Oral contraceptives	23	6.0	20	14.8	43	8.4
Condom	76	19.8	14	10.4	90	17.4
Tube ligation	90	23.5	17	12.6	107	20.6
Coitus interruptus	77	20.1	24	17.8	101	19.4
Vasectomy	2	0.5	1	0.7	3	0.6
Monthly injection	8	2.1	3	2.2	11	2.2
Calendar method	0	0.0	1	0.7	1	0.2
Total	458	70.4	192	29.6	650	100
	Non-menopausal (n:458)		Postmenopausal (n:192)			
	\bar{x}	SD	\bar{x}	SD		
Duration of contraceptive use (years)	9.84	6.73	13.90	9.50		
Number of pregnancy	3.26	1.90	3.83	2.46		
Number of children	2.44	1.11	2.78	1.31		
Duration of Menopause (years)	-	-	9.32	9.02		
Vaginal Bleeding Characteristic (ongoing for the last year)						
Number of pads in bleeding (daily)	5.27	3.25	2.60	2.93		
Bleeding duration (weekly)	5.34	1.63	3.72	2.20		
Frequency of bleeding (monthly)	2.06	1.00	1.81	1.54		

The chi-square analysis was performed by excluding the inadequate material group (**Table 3**), and a statistically significant difference was observed between the groups in terms of biopsy results, according to the menopausal status ($p < 0.05$). The Yates correction was conducted to understand the origin of this difference in distribution and was determined to commence from the "Hyperplasia (Atypia)" group ($\chi^2 = 8.318.485$, $p: 0.04$). Atypical endometrial hyperplasia is defined by the growth of unusual cells and is considered a cancer precursor. Therefore, the results of benign and atypical hyperplasia were evaluated by logistic regression analysis in terms of age, hormonal contraceptive use and duration, and AUB characteristics. The results depicting malignancy and inadequate material were not included in the analysis. The logistic regression analysis determined that the variables decided by the measurement co-

vered 73.6% of the total area between ± 1 standard deviation. Table 3 depicts that atypical endometrial hyperplasia in women aged 40–50 years increases 0.206 times (95% C.I. 0.055–0.773; $p < 0.05$), and 0.416 times (95% C.I. 0.160–1.238; $p < 0.05$) in women over 50 years of age, compared to women below 40 years. No significant difference was found in hormonal contraceptive use and its duration in terms of atypical endometrial hyperplasia ($p > 0.05$). Regarding AUB characteristics, increased use in the number of pads per day increases the atypical endometrial hyperplasia 1.569 times (95% C.I. 1.412–1.744; $p < 0.05$), the number of weekly bleeding 1.432 times (95% C.I. 1.295–1.582; $p < 0.05$), and the monthly frequency of bleeding 1.299 times (95% C.I. 1.099–1.536; $p < 0.05$) (Table 3). Besides, benign results in non-menopausal period included endometrial proliferation in 142 (35.6%), secretory endometrium in 121 (30.4%), endometrial polyp in 80 (20.1%), hyperplasia without atypia in 33 (8.3%), and endometritis in 22 (5.6%) women. Benign results in postmenopausal period showed endometrial proliferation in 17 (15.7%), secretory endometrium in 7 (6.4%), endometrial polyp in 49 (44.9%), hyperplasia without atypia in 18 (16.5%), endometritis in 3 (2.7%), and endometrial atrophy in 15 (13.8%) women.

Table 3: Comparison of Age, Use of Contraceptive, and AUB Characteristics in Non-menopausal and Postmenopausal Women in terms of Endometrial Biopsy Results

Grouped Biopsy Result	Non-menopausal (n:458)		Post-menopausal (n:192)		χ^2	P-value
	n	%	n	%		
Benign	398	86.9	109	56.8	7.635	0.029
Malignant	4	0.9	18	9.4		
Hyperplasia (Atypia)	41	9.0	32	16.6		
Inadequate material *	15	3.2	33	17.2		
	Regression Coefficient (B)		Standard Error		Odds Ratio [95% C.I.]	P-value
Age (years)						
Less than 40				1***		
40–50	1.578		0.674		0.206[0.055–0.773]	0.019
More than 50	0.808		0.521		0.416[0.160–1.238]	0.039
Use of Contraceptive Methods**						
No				1***		
Yes	0.268		0.102		0.70 [0.46–1.06]	0.096
Duration of Contraceptive Use (years) **	0.125		0.107		1.133[0.785–1.634]	0.504
Vaginal Bleeding Characteristic						
Number of pads in bleeding (daily)	0.451		0.054		1.569[1.412–1.744]	0.000
Bleeding duration (weekly)	0.359		0.051		1.432[1.295–1.582]	0.000
Frequency of bleeding (monthly)	0.262		0.085		1.299[1.099–1.536]	0.002

* Inadequate material group was excluded from Chi-Square analysis. **Just hormone-containing methods were included in the analysis. ***Reference value.

DISCUSSION

This study was designed to compare the results of the endometrial biopsy in women with AUB according to the presence of menopause. It is known that the risk of endometrial hyperplasia, carcinoma, and atrophy increases with menopause (9). It was observed in this study that

the atypical hyperplasia rates were higher in postmenopausal women as compared to that in non-menopausal women ($p < 0.05$) (Table 3). Deeba et al. (2016) evaluated the endometrial biopsy results of 110 women having a mean age of 62 with AUB in the postmenopausal period and found that atypical hyperplasia was present in 4.5% of the women (10). Besides AUB, conditions such as anovulatory cycle also increase endometrial hyperplasia, even in non-menopausal women (15). This is a significant observation as endometrial hyperplasia may be the precursor of endometrial cancer.

Endometrial hyperplasia, especially atypical hyperplasia, is reported to increase the risk of endometrial cancer (15). Women over 40 years of age have an increased risk of endometrial hyperplasia and cancer as compared to women younger than 40 years of age (16). The present study reported an increase in the rate of atypical hyperplasia with increasing age and AUB characteristics in women (Table 3). The main reason for this was the late hospital admission of postmenopausal women whom have AUB. Also, women in the non-menopausal period did not seek admission to the hospital for a substantial change in frequency, duration, or amount of bleeding during or between menstrual periods for a year. This shows that women lack information on AUB, both, in the non-menopausal and postmenopausal period, which in turn delays the diagnosis and treatment process.

Factors like age-dependent menopausal status, duration of menopause, and use of oral contraceptives increase the risk of endometrial cancer in women (17). According to the data, in the present study, 192 women were in the postmenopausal period for nearly nine years, and 10.6% of 650 women were found to use contraceptive methods containing both, estrogen and progesterone. Due to the use of these methods, an unmet estrogen effect is suspected in higher rates of endometrial hyperplasia that increases the risk of endometrial cancer in postmenopausal women in comparison to those in the non-menopausal women. The rate of endometrial cancer in the present study was 3.4% in women, regardless of the menopause presence. Saccardi et al. (2020) examined the

endometrial tissue in 435 women and determined that endometrial cancer affected 6.49% of postmenopausal women, independent of the AUB symptoms (18). In a retrospective study of women with AUB, the rate of endometrial cancer was found to be 0.3. However, in this study, the rate of women in postmenopausal period (14.2%) is lower than non-menopausal period (19). Deeba et al. (2016) observed endometrial cancer in 12.7% women with AUB in the postmenopausal period (n: 110) (10). From these results, it is known that endometrial cancer rates of women are affected according to their menopausal status, age and the presence of AUB.

In our study, the average menopausal age of Turkish women is compatible with the average menopausal age of women across the country (20). However, regardless of other factors, it is seen in this study that women with AUB postponed their admission to the hospital for the last year. In this study, it is understood that women have a lack of information about AUB.

Examination of the benign changes ascertained that secretory endometrium and endometritis were found to affect women in the non-menopausal period more as compared to those in the postmenopausal period. Secretory endometritis is not likely to occur in women during the postmenopausal period. However, it was observed in seven women, presumably due to the onset of menopause. The inexistence of proliferative endometrial outcome is an expected result because of the hormonal changes in the endometrium of women in the non-menopausal period. Likewise, it is an expected result that the rate of endometritis is higher in younger women than in menopausal women, due to hormonal changes due to the menstrual cycle, pregnancy, childbirth and the possibility of having a more active sexual intercourse. Polyps were found to affect more women in the postmenopausal period than those in the non-menopausal period. Polyp rates vary between 1.34 and 7% in several studies (9, 10, 21). The present study also recognized considerably high polyp rates. The rate of inadequate material in this study is 7.4% regardless of the groups. Other studies with similar samples size report inadequate material in 8.7% of all study

participants (18, 19). Inadequate material may be high in women during menopause due to the endometrial atrophy. Above and beyond, an endometrial biopsy is a surgical procedure requiring patient consent. The approach necessitates experienced personnel who must diagnose the condition accurately.

A higher number of atypical hyperplasia was determined in women who were in the postmenopausal period as compared to those in the non-menopausal period in this study.

Careful evaluating of women with atypical hyperplasia is essential to exclude the risk of malignancy. Endometritis affected more women in the non-menopausal period, while polyp was identified in higher numbers in the postmenopausal period. Moreover, the rate of inadequate material is also a significant matter among women with AUB. Therefore, the fact that the endometrial biopsy is not concluded due to insufficient material is costly and an examination of this cost would be quite logical.

It was determined that the knowledge level of women about AUB was insufficient. Although the study participants experienced AUB symptoms since the last year, they delayed the admission to the hospital. Therefore, women must be informed and educated for AUB.

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