# HISTOPATHOLOGICAL CHANGES OF THE ENDOMETRIUM IN PATIENTS WITH ABNORMAL UTERINE BLEEDING AND ASSOCIATION WITH SOME RISK FACTORS

Ana Kocevska<sup>1,5</sup>, Dimce Zafirov<sup>2,5</sup>, Gordana Petrushevska<sup>3,5</sup>, Kristina Skeparovska<sup>1,5</sup>, Slavica Shubeska - Stratrova<sup>4,5</sup>

<sup>1</sup>Special hospital for gynecology and obstetrics "Mother Theresa" Chair – Skopje, R. North Macedonia <sup>2</sup>Institute of Preclinical and Clinical Pharmacology and Toxicology,

<sup>3</sup>Institute of Pathology,

<sup>4</sup>University Clinic of Endocrinology, Diabetes and Metabolic Dysorders, <sup>5</sup>Faculty of Medicine, Ss. Cyril and Methodius University in Skopje, R. North Macedonia

## Abstract

Abnormal uterine bleeding is a complex gynecological problem, especially in the perimenopausal and postmenopausal period. Etiology may be organic (endometrial polyp, hyperplasia, myoma, endometrial atrophy, carcinoma) or non-organic (dysfunctional uterine bleeding).

To analyze the histopathological findings of samples of fractionated explorative curettage in patients with abnormal uterine bleeding and to investigate certain risk factors for their occurrence (age, obesity, hypertension, diabetes).

This was a prospective study comprising a total of 104 subjects. They were divided into two groups: 54 women in postmenopausal age and 50 in premenopausal age. The data were collected by interviewing and analyzing the findings from histopathological analyses of samples obtained by fractional explorative curettage. The following anamnestic data were analyzed: age, history of hypertension and diabetes. The study was performed in the Special Hospital for Gynecology and Obstetrics "Mother Theresa" - Chair.

The most common pathological finding in both groups was endometrial polyp (in 39.5% of postmenopausal and 46.9% of premenopausal women). In 4 participants (5.7% of the total), endometrial adenocarcinoma was diagnosed. The mean age of patients was 57 years in the postmenopausal group and 43 years in the premenopausal group. The average BMI (Body Mass Index) was 33 in the postmenopausal group and 25 in the premenopausal group. Hypertension was detected in 64.8% of postmenopausal women and in 34% of premenopausal women. 13% of postmenopausal women were diagnosed with diabetes. It was detected in 12% of premenopausal women.

Fractional explorative curettage is an important diagnostic procedure for prompt and timely diagnosis of premalignant and malignant changes of the female genital tract. We detected endometrial adenocarcinoma in 7,4% of the postmenopausal patients and in 4% of premenopausal patients with abnormal uterine bleeding. It is especially important to highlight obesity and hypertension as risk factors for abnormal uterine bleeding and endometrial pathology.

*Key words*: abnormal bleeding, uterus, fractional explorative curettage

# Introduction

Abnormal uterine bleeding is a complex gynecological problem, especially in the perimenopausal and postmenopausal period in women. It is defined as any bleeding that deviates from the normal menstrual cycle in terms of regularity, volume, frequency or duration, occurring in the absence of pregnancy [1].

The International Federation of Gynecology and Obstetrics (FIGO) has defined a classification system for abnormal uterine bleeding called PALM-COEIN (polyp, adenomyosis, leiomyoma,

malignancy and hyperplasia). The prevalence is 9-14% during the lifetime and it is the cause of 25% of surgeries performed on women [2, 3].

The etiology may be organic (endometrial polyp, hyperplasia, fibroids, endometrial atrophy, cancer) or non organic (dysfunctional uterine bleeding) [4]. Dysfunctional bleeding is more common in younger patients, while endometrial atrophy and organic lesions are more common in older patients [5]. Endometrial polyps are one of the most common pathologies in patients with abnormal bleeding and occur in both pre- and postmenopausal patients [6].

Endometrial hyperplasia is an abnormal proliferation of the endometrial glands and stroma, and is associated with an increased risk of endometrial cancer [7].

Patients with a history of anovulation, obesity, hypertension, diabetes, and the use of exogenous hormones are at an increased risk of endometrial hyperplasia and adenocarcinoma [1].

The endometrium is an easily accessible tissue for sampling for histopathological evaluation. Dilatation and curettage is the standard procedure and method of choice for endometrial sampling [8].

#### **Objectives**

To analyze the histopathological findings of the samples from fractionated exploratory curettage in patients with abnormal uterine bleeding and to determine the presence of certain risk factors in the examined groups (age, obesity, hypertension, diabetes).

#### **Material and Methods**

This was a prospective study comprising a total of 104 subjects who underwent fractional explorative curettage due to abnormal uterine bleeding. Subjects were divided into two groups: 54 women in postmenopausal age and 50 in premenopausal age. Data were collected through interviews and analysis of findings from histopathological analyses of samples obtained by fractional explorative curettage.

Fractional explorative curettage was performed under intravenous anesthesia, with a sample from the endocervix and a sample from the endometrium. Samples were immediately fixed in 10% formalin and sent to a histopathological laboratory.

1

Analysis of the obtained histopathological findings and their distribution in the two examined groups was performed.

The following anamnestic data were analyzed: age, history of hypertension and diabetes.

Weight and height were measured in all women. The Body Mass Index (BMI) was calculated with the following formula: body weight (kg) / body height (m<sup>2</sup>) The study was performed at the Special Hospital for Gynecology and Obstetrics "Mother Theresa" - Chair. Histopathological analyzes were performed at the Institute of Pathologic Anatomy at the Faculty of Medicine in Skopje.

#### Results

The most common pathological change of the endometrium in both groups was endometrial polyp (in 38.9% of postmenopausal and 36% of premenopausal respondents). Endometrial adenocarcinoma was diagnosed in 6 patients (5.8% of the total number). It was more present in the postmenopausal group (in 7.4%) than in the premenopausal group (4%). 27.8% of postmenopausal women were diagnosed with endometrial atrophy, and there was none in the premenopausal group. Dysfunctional bleeding due to prolonged and inadequate estrogenic action was present in 2 patients from the postmenopausal group (3.7%) and 8 respondents from the premenopausal group (26%). In the postmenopausal group, endometrial hyperplasia without atypia was detected in 2 cases (5.2%) (Table 1).

<b>Table 1</b> : Distribution of both groups a	ccording to histopatholo	gical findings
	Postmenopausis	Premenopausis
Endometrial atrophy	15 (27.8%)	0
Endometrial polyp	21 (38.9%)	18 (36%)
Endometrial hyperplasia without atypia	2 (5.2%)	13 (26%)
Prolonged and inadequate estrogenic action	2 (3.7%)	8 (16%)
Normal	4 (7.4%)	1 (2%)
Endometrial adenocarcinoma	4 (7.4%)	2 (4%)
Cervical dysplasia	2 (3.7%)	0
Cervical polyp	3 (5.6%)	5 (10%)
Deficient secretory phase	0	3 (6%)
Chronic cervicitis	1 (2.6%)	0
	total 54	total 50

<b>Table 1</b> · Distribution of both $\sigma$	roups according to	o histonatholo	oical	findings
<b>Table 1</b> . Distribution of both g	roups according to	0 mstopatholo	gicai	munige

The average age of the patients was 50 years. In the postmenopausal group the mean age was 57 years, and in the premenopausal group 43 years. The most common age group was 51-55 years (total of 32 respondents or 30.8%).

The mean BMI (Body mass index) value was 30, with 33 in the postmenopausal group and 25 in the premenopausal group.

al	ble 2: Distribution	of both groups according to BM
	BMI	
	<25	12 (11.5%)
	25-30	34 (32.7%)
	30-35	38 (36.5%)
	>35	20 (19.2%)
	total	104 (100%)

#### Тε ΛI

Hypertension was found in 64.8% of postmenopausal women. It was detected in 34% of premenopausal women (Table 3).

Tabl	e 3:	Distribution	according	to the	pres	sence of	hyperten	sion

Hypertension	Postmenopausis	Premenopausis
yes	35(64.8%)	17(34%)
no	19(35.2%)	33(66%)
total	54	50

13% of postmenopausal women were diagnosed with diabetes. It was detected in 12% of premenopausal women (Table 4).

**Table 4**: Distribution according to the presence of diabetes

Diabetes mellitus	Postmenopausis	Premenopausis
yes	7 (13%)	6 (12%)
no	47 (87%)	44 (88%)
total	54	50

### Discussion

Abnormal uterine bleeding is one of the most common gynecological problems, which can occur at any age, but is most common in the perimenopausal and postmenopausal age. In our study participated 104 patients, with a mean age of 50 years. The most common age group was 51-55 years (32 patients or 30.8%).

Out of a total of 104 subjects, 39 received a histopathological diagnosis of endometrial polyp: 21 (38.9%) of postmenopausal and 18 (36%) of premenopausal women.

Endometrial polyps are common, and their prevalence increases with age. A screening study of the general female population found that they were more common in postmenopausal women (11.8%) than in premenopausal women (5.8%). Most endometrial polyps are benign. In a meta-analysis of their malignant potential, the risk was found to be highest in postmenopausal women with vaginal bleeding [9].

In a Turkish study, the presence of endometrial polyp was found in 9 out of 45 subjects (20%), and 2 of those 9 showed the presence of hyperplasia without atypia [10]. In our study, all polyps were free of hyperplasia. Endometrial hyperplasia is a common cause of abnormal bleeding. It occurs due to prolonged exposure to unopposed estrogen and is a premalignant condition that can lead to the development of endometrial cancer. It is not well known how long it takes for cancer to develop, but a study by Lacey et al. found an average time of 6 years for cancer to develop, in all types of hyperplasia [11].

In our study we detected 15 cases of endometrial hyperplasia without atypia, of which 13 were in the premenopausal group and 2 in the postmenopausal group.

Diagnostic curettage should be performed in all postmenopausal patients where a thickened endometrium or endometrial polyp has been detected by ultrasound, due to the possibility of the presence of atypical hyperplasia and cancer at the same time [12].

Endometrial adenocarcinoma is the most common gynecological malignancy. It occurs more often in postmenopausal women. About 40% of cases are associated with obesity in patients [13].

Endometrial cancer is also associated with excessive estrogen exposure, high blood pressure, and diabetes [14].

In our study we detected Endometrial adenocarcinoma in 6 patients (5.8% of the total number). It was more common in the postmenopausal group (7.4%) than in the premenopausal group (4%).

It is especially important to highlight obesity as a significant risk factor for endometrial pathology. In our study, 38 subjects (36.5% of the total number) were obese, and 20 (19.2% of the total number of subjects) were severely obese (BMI over 35).

Hypertension was found in 64.8% of postmenopausal women. It was detected in 34% of premenopausal women. In a study by Giordano et al., it was noted that most of their subjects with malignant endometrial polyps had risk factors such as hypertension, obesity, and unopposed estrogen therapy [15]. In our study, we also analyzed the presence of diabetes mellitus. 13% of postmenopausal

women were diagnosed with diabetes. It was detected in 12% of premenopausal women. A meta-analysis by Zhang et al. found an increased risk of endometrial cancer in patients with diabetes [16].

### Conclusion

To emphasize the importance of diagnostic fractional explorative curettage, in order to quickly and timely diagnose of premalignant and malignant changes of the female genital tract. Particular importance is given to the postmenopausal age when no bleeding should occur and when organic causes of abnormal bleeding are more common, especially cancer as the most severe pathology.

We detected endometrial adenocarcinoma in 7,4% of the postmenopausal patients and in 4% of premenopausal patients with abnormal uterine bleeding. It is especially important to highlight obesity and hypertension as significant risk factors for endometrial pathology. In our study, 38 subjects (36.5% of the total number) were obese, and 20 (19.2% of the total number of subjects) were severely obese (BMI over 35).

Hypertension was found in 64.8% of postmenopausal women with abnormal uterine bleeding. It was detected in 34% of premenopausal women.

## **References:**

- 1. Munro MG, Critchley HO, Broder MS, et al. FIGO classification system (PALM-COEIN) for causes of abnormal uterine bleeding in nongravid women of reproductive age. Int J Gynaecol Obstet. 2011; 113, 3-13.
- 2. Albers JR, Hull SK, Wesley RM. Abnormal uterine bleeding. Am Fam Physician. 2004;69(8):1915-26.
- 3. Sweet MG, Schmidt-Dalton TA, Weiss PM, Madsen KP. Evaluation and management of abnormal uterine bleeding in premenopausal women. Am Fam Physician. 2012;85(1):35-43
- 4. Heller DS. Pathologic basis for abnormal uterine bleeding with organic uterine pathologies. Menopause. 2011;18(4):412-5.
- Mazur MT, Kurman RJ. Normal endometrium and infertility evaluation. In: Mazur MT, Kurman RJ, editors. Diagnosis of endometrial biopsies and curettings: A practical approach. 2nd ed. New York: Springer Verlag; 2005. P. 7-33.
- 6. Salim S, Won H, Nesbitt-Hawes E, et al. Diagnosis and management of endometrial polyps: a critical review of the literature. J Minim Invasive Gynecol. 2011; 18, 569-81.
- Li XC, Song WJ. Endometrial intraepithelial neoplasia (EIN) in endometrial biopsy specimens categorized by the 1994 World Health Organization classification for endometrial hyperplasia. Asian Pac J Cancer Prev. 2013; 14, 5935-9.
- 8. Dreisler E, Stampe Sorensen S, Ibsen PH, Lose G. Prevalence of endometrial polyps and abnormal uterine bleeding in a Danish population aged 20-74 years. Ultrasound Obstet Gynecol 2009;49:229-33.
- 9. Lieng M, Istre O, Qvigstad E. Treatment of endometrial polyps: a systematic review. Acta Obstet Gynecol Scand 2010;89:992-1002.
- Acmaz G, Aksoy H, Albayrak E, et al. Evaluation of endometrial precancerous lesions in postmenopausal obese women – a high risk group?. Asian Pac J Cancer Prev 2014;15(1). 195-198.
- 11. Lacey JV Jr, Sherman ME, Rush BB, et al. Absolute risk of endometrial carcinoma during 20year follow-up among women with endometrial hyperplasia. J Clin Oncol 2010;28, 788-92
- 12. International Agency for Research on Cancer. World Cancer Report. World Health Organization. Chapter 5.12., 2014.
- 13. General Information About Endometrial Cancer. National Cancer Institute https://www.cancer.gov/types/uterine/patient/endometrial-treatment-

pdq#section/all?redirect=true (23.09.2020)

- 14. Nappi L, Indracollo I. Are diabetes, hypertension and obesity independent risk factors for endometrial polyps. J Minim Invasive Gynecol 2009; 16(2): 157-162.
- 15. Giordano G, Gnetti L, Merisio C, Melpignano M. Postmenopausal status, hypertension and obesity as risk factors for malignant transformation in endometrial polyps. Maturitas 2007;56: 190-197.
- 16. Zhang ZH, Su PY, Hao JH, Sun YH. The role of preexisting diabetes mellitus on incidence and mortality of endometrial cancer: a meta analysis of prospective cohort studies. Int J Gynecol Cancer 2013;23(2): 294-303.