

ENDOMETRIAL PATHOLOGICAL CHANGES IN PERIMENOPAUSE AND POSTMENOPAUSE - ASSOCIATION WITH SOME ANAMNESTIC AND ULTRASONOGRAPHIC PARAMETERS

Ana Kocevaska^{1,6}, Dimche Zafirov^{2,6}, Gordana Petrushevska^{3,6}, Bashkim Ismaili¹, Kristina Skeparovska^{1,6}, Dimitar Georgiev¹, Shenol Tahir^{4,6}, Tosho Plasheski^{5,6}

¹ Specialized Hospital for Gynecology and Obstetrics "Mother Teresa" – Skopje, R.North Macedonia

² Institute of Preclinical and Clinical Pharmacology and Toxicology, Faculty of Medicine, Ss. Cyril and Methodius University in Skopje, R.North Macedonia

³ Institute of Pathology, Faculty of Medicine, Ss. Cyril and Methodius University in Skopje, R.North Macedonia

⁴ University Clinic for Surgical Diseases "St. Naum Ohridski" – Skopje, R.North Macedonia

⁵ University Clinic for Endocrinology, Diabetes and Metabolic Disorders – Skopje, R.North Macedonia

⁶ Faculty of Medicine, University Ss. Cyril and Methodius University in Skopje, R.North Macedonia

Abstract

Atypical endometrial hyperplasia is preneoplastic condition that precedes endometrioid adenocarcinoma. Postmenopausal women should not have bleeding; the thickness of the endometrium is normally below 5 mm and if it is above, the presence of a polyp, hyperplasia or cancer is suspected.

To determine the histopathological changes of the endometrium, the prevalence of functional and organic changes and their association with history of previous childbirths and abortions, presence of bleeding, intensity of bleeding, anteroposterior uterine diameter and endometrial thickness.

The study was performed in the Specialized Hospital for Gynecology and Obstetrics "Mother Teresa" - Skopje and involved a total of 120 respondents who underwent fractionated explorative curettage due to a medical indication.

They were divided into 2 groups: with functional and organic changes of the endometrium. Ultrasonographic measurement of anteroposterior diameter of uterus and endometrial thickness was performed.

The prevalence of functional changes was 30% and of organic changes 70%. The most common histopathological diagnosis was an endometrial polyp (45% of women). The mean value of endometrial thickness was 7.9 mm in the functional changes group and 13.6 mm in the organic changes group; this difference was statistically significant ($p < 0.0001$).

Perimenopausal patients had a significantly longer duration of bleeding than those in postmenopause ($p = 0.0009$).

Endometrial adenocarcinoma was present in 3% of perimenopausal and in 5% of postmenopausal patients. Endometrium was significantly thicker in women with organic changes than in those with functional changes.

Perimenopausal patients had a significantly longer duration of bleeding, more intensive bleeding, thicker endometrium and greater anteroposterior uterine diameter than those in postmenopause.

Keywords: fractionated explorative curettage, endometrial thickness, uterine bleeding.

Introduction

Dilatation and curettage is the gold standard technique for endometrial sampling. It is performed by dilation of the cervical canal in order to be able to insert the curette into the endometrial cavity. It is performed under general anesthesia [Figure 1].

Material is taken from the anterior and posterior endometrial surface with a curette by "scratching". By using this method, samples can be taken from the endometrial, but also from the endocervical mucosa (fractionated curettage).

Fractional sampling is useful for evaluating possible endocervical pathology as well as the presence of endocervical extension of endometrial adenocarcinoma. Dilatation and curettage are commonly used when it is necessary to take a larger sample of the endometrium in order to rule out a significant pathology or when it is necessary to remove a larger endometrial volume in patients with heavy bleeding [1–3]. Possible complications of this intervention are: hemorrhage, infection or perforation, each occurring at a rate of 4 to 6 per 1000 procedures [4].

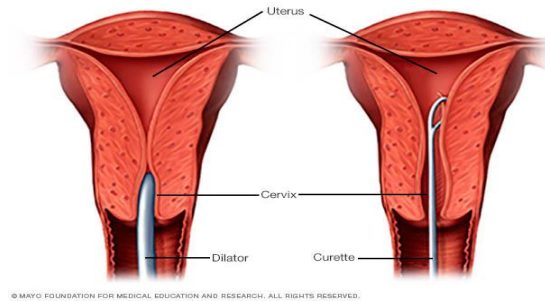


Figure 1. Dilatation and curettage

Menopause is the period in a woman's life when menstrual cycles stop and the reproductive period ends. A few years before menopause, menstrual cycles typically become irregular, last longer or shorter than normal, or menstrual bleeding is reduced or increased [6].

A postmenopausal woman should not have genital bleeding and any bleeding is an alarming symptom to be examined to rule out malignancy. In a meta-analysis of Megane Clarke *et al.*, 129 studies were analyzed with a total of 40,790 patients and found that postmenopausal bleeding occurred in approximately 90% of patients with endometrial cancer, but only 9% of women with postmenopausal bleeding were diagnosed with endometrial cancer [7].

The term "dysfunctional uterine bleeding" is used when there is no structural (organic) cause for abnormal bleeding and it occurs due to anovulation or defective ovulation [8].

The normal thickness of the endometrium during menstruation is 2-4 mm, in the early proliferative phase 5-7 mm, preovulatory up to 11 mm, in the secretory phase 7-16 mm. After curettage or after miscarriage, it should be <5 mm; if it is thicker, it means that there are retained products of conception or residual masses [9].

In postmenopause the thickness of the endometrium is normally less than 5 mm when it is very likely to rule out pathological change of the endometrium, and if it is greater than 5 mm, the presence of a polyp, hyperplasia or cancer is possible [10,11].

Endometrial hyperplasia (EH) is a condition characterized by the proliferation of endometrial glands in various shapes and sizes, as well as an increased ratio of glands and stroma in favor of the glands. It is a consequence of prolonged action of estrogens, without the suppressive action of progesterone. It is most commonly diagnosed during the perimenopausal period when anovulatory cycles are frequent. In the younger population it is most commonly associated with polycystic ovarian syndrome (PCOS), obesity or menstrual disorders [12].

In 2014, the WHO changed the classification of EH into 2 categories: benign endometrial hyperplasia (not atypical) and atypical endometrial hyperplasia/endometrial intraepithelial neoplasia [13]. Atypical endometrial hyperplasia is a preneoplastic condition that precedes the most common malignant tumor of the uterus, endometrioid adenocarcinoma (type I endometrial cancer, 80% of endometrial cancers) [14].

Endometrial carcinoma (EC) occurs as a result of abnormal growth of endometrial cells that acquire the ability to invade and metastasize to other parts of the body [15].

It is the most common cancer of the female reproductive tract in developed countries and the third most common cause of cancer death in women (behind ovarian and cervical cancer) [16]. Its incidence is rising, probably due to an increasing number of older people and rising obesity rates. In obese women excessive adipose tissue increases the conversion of androstenedione to estrone.

High levels of estrone in the blood cause anovulation and the endometrium is exposed to continuously high levels of estrogen [17]. The most common type of endometrial cancer is endometrioid adenocarcinoma (75% to 80%). Other non-endometrioid tumor types are: mucinous carcinomas (5%), clear cell carcinomas (5%), papillary serous carcinomas (4%), and squamous cell carcinomas (1%). These types are rare but have a more aggressive course [18]. Endometrial cancer can occur in premenopausal (25%) and postmenopausal (75%) women.

The average age at the time of diagnosis is 61 years [18]. EC is often ultrasonographically seen as irregular thickening of the endometrium with areas of polypoid mass-like soft tissue [Figure 2].



Figure 2. Ultrasonographic appearance of the endometrial carcinoma [19]

Endometrial polyps (EPs) are benign proliferations of the endometrium that contain varying amounts of glandular tissue, connective tissue and blood vessels. The morphological diversity of EPs is a reflection of the type of endometrium they originate from, so they can range from atrophic to hyperplastic and carcinomatous [20].

Clinically, these lesions cause thickening of the endometrium and abnormal bleeding from the uterus. Asymptomatic EPs can be detected by a routine ultrasound examination or by infertility investigations [21]. A Danish screening study of the general population showed a higher prevalence of EPs in postmenopausal women (11.8%) than in premenopausal women (5.8%) [22]. Most EPs are benign. In a meta-analysis of their malignant potential, the risk was found to be highest in postmenopausal women with vaginal bleeding (2.3%).

The risk for presence of carcinomatous polyp in asymptomatic women was 0.3%. The prevalence of atypical hyperplastic polyps was 1.2% in asymptomatic and 2.2% in symptomatic patients; $p < 0.005$ [23]. Postmenopausal women with a polyp have a higher risk of polyp malignancy than premenopausal women with a polyp [24].

Objectives

To determine the histopathological changes of the endometrium that occur during the period of perimenopause and postmenopause, to determine the prevalence of functional and organic changes and their association with the history of previous childbirths and abortions, presence of uterine bleeding and intensity of bleeding, anteroposterior diameter of uterus (APd) and endometrial thickness.

Material and methods

The study was a prospective observational cohort and was performed in the Specialized Hospital for Gynecology and Obstetrics "Mother Teresa" - Skopje, in cooperation with the Institute of Pathological Anatomy at the Faculty of Medicine – Skopje.

The study involved a total of 120 respondents who underwent fractionated explorative curettage due to a medical indication (abnormal bleeding or ultrasound-diagnosed endometrial abnormality). They were divided into 2 groups: with functional changes of the endometrium (prolonged and inadequate estrogenic action, deficient secretory phase, endometrial atrophy) and organic changes (endometrial polyp, endometrial hyperplasia without atypia, endometrial adenocarcinoma).

Fractionated explorative curettage was performed under general intravenous anesthesia. The material (from endocervix and endometrium) in 2 vials with 10% formalin was sent to histopathological analysis at the Institute of Pathological Anatomy at the Faculty of Medicine - Skopje. Anamnestic data were taken from all respondents.

Ultrasonographic measurements of anteroposterior diameter of uterus (APd) and endometrial thickness were performed with TOSHIBA Xario 200 ultrasound device, using endovaginal probe 11C3, with frequency of 7.0 MHz.

Results

The prevalence of functional changes was 30% (36 patients) and of organic changes 70% (84 patients) [Table 1]. Half of the patients (60) were perimenopausal and the other 60 were postmenopausal. The most common pathological change of the endometrium was an endometrial polyp and it was present in 45% of respondents. Endometrial hyperplasia without atypia was present in 23.3% of perimenopausal and 15% of postmenopausal women.

Endometrial adenocarcinoma was present in 3% of perimenopausal and 5% of postmenopausal women. Endometrial atrophy was detected only in postmenopausal women (26.7%) and dysfunctional abnormalities (inadequate and prolonged estrogenic action, deficient secretory phase) were present only in perimenopausal patients (26.7%) [Table 2].

Table 1. Distribution of organic and functional histopathological changes

group	n
functional changes	36 (30%)
organic changes	84 (70%)

Table 2. Distribution of histopathological changes in perimenopause and postmenopause

Histopathological diagnosis	groups			p-level
	n	perimenopause	postmenopause	
Endometrial polyp	54	27 (45%)	27 (45%)	X ² =26.99 **p=0.00006
Endometrial atrophy	16	0	16 (26.67%)	
Endometrial hyperplasia without atypia	23	14 (23.33%)	9 (15%)	
Endometrial adenocarcinoma	8	3 (5%)	5 (8.33%)	
Prolonged and inadequate estrogenic action	15	12 (20%)	3 (5%)	
Deficient secretory phase	4	4 (6.67%)	0	

X² (Pearson Chi-square)

**p<0.01

Patients with functional and organic changes had similar age (mean 53.3 vs. 52.5 years, $p=0.64$). In the group of postmenopausal respondents, the duration of postmenopause was not significantly different between those with functional and organic changes (median 7 vs. 8 years, $p = 0.47$).

The presence of uterine bleeding and its duration and intensity was higher in the group with organic changes compared to the group with functional changes, but without a statistical significance (median 10 vs. 7 days, $p=0.3$).

Ultrasonographic parameters (anteroposterior diameter of the uterus and endometrial thickness) had higher values in patients with organic changes of the endometrium. Uterine APd had a mean value of 41.3 mm in the group with functional and 45.2 mm in the group with organic changes of the endometrium, but without a statistically significant difference between the two groups ($p=0.08$) [Table 3]. The mean value of endometrial thickness was 7.9 mm in the functional changes group and 13.6 mm in the organic changes group, with a difference of 5.7 mm that was statistically significant ($p < 0.0001$) [Table 3].

Table 3. Uterine APd and endometrial thickness in the functional and organic change groups.

variable	Type of HPA changes		p-level
	functional	organic	
Uterine APd (mm)			
mean \pm SD	41.3 \pm 11.6	45.2 \pm 10.9	t=1.76
min – max	25 – 70	28 – 78	p=0.08
Endometrial thickness (mm)			
mean \pm SD	7.9 \pm 2.6	13.6 \pm 4.5	t=7.04
min – max	4 – 14	7 – 26	***p=0.000000

t(Student t-test)

***p<0.0001

One patient with functional and 5 with organic changes were nulliparous. Most of the patients in both groups have given birth to two children (33.3% vs. 47.6%). 41.7% of women in the functional change group and 59.5% in the organic change group denied previous abortions and the similar number of them reported that they have had one previous abortion (22.2% vs. 17.9%).

These differences were without a statistical significance.

Half of the patients (60) were perimenopausal and the other 60 were postmenopausal. Perimenopausal patients were significantly younger than postmenopausal (46.7 vs. 58.7 years; $p < 0.0001$).

Nulliparous were 3.3% of perimenopausal and 6.7% of postmenopausal patients. Most of the patients in both groups have given birth to two children (38.3% perimenopausal vs. 48.3% postmenopausal patients). 66.7% of perimenopausal and 41.7% of postmenopausal patients did not have previous abortions.

Regarding the number of abortions, perimenopausal patients usually had one abortion (16.7%) and postmenopausal usually had two abortions (23.3%). Perimenopausal and postmenopausal women did not differ significantly in terms of the number of childbirths ($p = 0.92$), while they differed significantly in terms of the number of abortions.

Postmenopausal patients had a significantly higher number of previous abortions ($p = 0.007$).

Perimenopausal patients had a significantly longer duration of uterine bleeding than postmenopausal patients (median 10 vs. 3.5 days; $p = 0.0009$) [Table 4].

Table 4. Duration of bleeding in peri- and postmenopausal patients.

Number of days of bleeding	perimenopause	postmenopause	p-level
mean ±SD	10.83 ± 9.2	6.37 ± 8.1	Z=3.32
median (IQR)	10 (5 – 14.5)	3.5 (0 – 7)	***p=0.0009

Z (Mann-Whitney U test)

***p<0.0001

Patients in perimenopause had significantly more intensive bleeding than those in postmenopause (p=0.00008). 41.7% of perimenopausal and 18.3% of postmenopausal patients had a moderate intensity of bleeding. Heavy bleeding was present in 15% of perimenopausal women and in none of postmenopausal. Uterine APd had a mean value of 50.7 mm in perimenopausal and 37.3 mm in postmenopausal women. The difference of 13.4 mm was confirmed as statistically significant (p <0.0001) [Table 5].

The mean value of endometrial thickness was 13.6 mm in perimenopausal and 10 mm in postmenopausal patients. The difference of 3.6 mm was confirmed as a statistically significant (p=0.00011) [Table 5].

Table 5. Uterine APd and endometrial thickness in peri- and postmenopausal patients.

variable	perimenopausal	postmenopausal	p-level
Uterine APd (mm)			
mean ±SD	50.66 ± 8.04	37.33 ± 9.9	t=8.08
min – max	36 – 78	25 – 72	***p=0.000000
Endometrial thickness (mm)			
mean ±SD	13.57 ± 4.9	10.28 ± 4.1	t=3.99
min – max	5 – 26	4 – 24	***p=0.00011

t(Student t-test)

***p<0.0001

Discussion

In our study we included 120 women with abnormal uterine bleeding or asymptomatic with ultrasonographically detected changes of the endometrium, and thus an indication for histopathological analysis.

We performed fractionated explorative curettage under general intravenous anesthesia. In our hospital this is a standard procedure for taking a sample of endometrium, and less often by hysteroscopy in the operating room.

There are several methods for taking an endometrial sample. Dilatation and curettage is the most widely used method, but it has become less favorable due to the anesthesiological and surgical risks of complications.

Endometrial aspiration biopsy has largely replaced dilatation and curettage because it is a safe and reliable outpatient procedure, without use of general anesthesia, easy to perform, and with high sensitivity and specificity in the detection of endometrial hyperplasia and carcinoma [25,26].

Hwang *et al.* performed a study on 250 subjects diagnosed with endometrial hyperplasia by taking an endometrial sample by aspiration biopsy (150 subjects) and dilatation and curettage (100 subjects), followed by a hysterectomy in the next 6 months after diagnosis [27].

The concordance between the sample taken by aspiration biopsy and that taken by hysterectomy was 41.3%, while the concordance between the sample taken by dilatation and curettage and the one taken by hysterectomy was 51%. Patients in whom the preoperative sample was taken by dilatation and curettage had a significantly lower detection of more severe histopathological findings in the hysterectomy specimen

(21%) than patients whose preoperative specimen was taken by aspiration biopsy (36.7%). This difference was statistically significant ($p=0.008$) [27].

When the final diagnosis (after hysterectomy) was endometrial cancer, there were significantly fewer upgrades after dilatation and curettage than after aspiration biopsy (15% vs. 27.3%, $p=0.022$). As a conclusion, dilatation and curettage was more accurate diagnostic procedure than aspiration biopsy [27].

In our study, endometrial changes were benign in 112 of the patients (93.3%) and endometrial adenocarcinoma was present in 8 of them (6.7%). The most common histopathological change was endometrial polyp, found in 54 subjects (45%). It was equally present in perimenopausal and postmenopausal women. EPs are a common pathology, occurring in 25% of the general female population, most commonly in perimenopausal and postmenopausal women, and often are associated with abnormal uterine bleeding [28].

Some polyps may regress spontaneously and it is not necessary to perform an emergency polypectomy to avoid surgical and anesthetic risk.

The study by Yuksel *et al.* identified the following factors that are associated with spontaneous regression: age <45 years, premenopausal period, polyp size <2 cm and the presence of abnormal uterine bleeding. In this study, a regression rate of 23% was found only in premenopausal women and all postmenopausal patients had persistent polyps [29].

Postmenopause is considered a risk factor for development of endometrial neoplasia in a polyp. Fernandez-Parra *et al.* in their study detected a prevalence of 1.5% carcinomatous polyps only in symptomatic postmenopausal women (with bleeding), but not in asymptomatic and premenopausal women [30].

In one multicenter Italian study of 1152 asymptomatic and 770 symptomatic postmenopausal women with hysteroscopic polypectomy, Ferrazzi *et al.* detected only 1 case (0.1%) of a carcinomatous polyp present in an asymptomatic patient. This prevalence was 10-fold lower than in symptomatic patients ($p<0.0001$).

The prevalence of polyps with atypical hyperplasia was 1.2% in asymptomatic women and 2.2% in symptomatic women ($p<0.005$) [31].

Endometrial hyperplasia is clinically significant as the cause of abnormal uterine bleeding as well as of its association with endometrial cancer [12]. EH most often occurs in perimenopause as a consequence of anovulatory menstrual cycles [32,33].

In the reproductive period, EH is relatively rare and occurs predominantly in women who are overweight and have polycystic ovary syndrome [32]. In postmenopausal women, EH occurs as a result of exogenous or endogenous hyperestrogenemia that is not opposed by progesterone, as a consequence of estrogen therapy or by peripheral conversion of androgens to estrogens in adipose tissue [32,33].

In the study by Milosevic *et al.*, premenopausal patients had a pathohistologically verified higher incidence of EH without atypia than postmenopausal patients (22.4% in premenopause vs. 10.5% in postmenopause) and this difference was statistically significant ($p<0.01$).

Atypical EH was more common in postmenopausal (3.3%) than in premenopausal patients (0.9%) and this difference was statistically significant ($p<0.05$). The same study found that EH was a significantly more common cause of abnormal bleeding in premenopausal patients (in 23.4%) than in postmenopausal patients (in 3.7%) [34].

It is important, especially in these risk groups, to perform an endometrial examination to identify the presence of EH with atypia, which is precancerous lesion of the endometrial cancer [35]. In our study, EH without atypia was present in 9 (15%) of postmenopausal women and 14 (23.3%) of perimenopausal women.

We detected endometrial adenocarcinoma in 3 women (5%) in perimenopause and 5 women (8.3%) in postmenopause. In the study by Milosevic *et al.*, the presence of endometrial carcinoma (EC) was found in 1.4% of premenopausal and 18.9% of postmenopausal women.

Uterine bleeding caused by endometrial cancer was significantly more common in postmenopausal women than in premenopausal women.

According to the same study, in the postmenopausal period there is a higher risk of developing both endometrioid and non-endometrioid type of EC (type I and type II), as well as the occurrence of cancer localized in the endometrial polyp [34].

In a meta-analysis by Megane Clarke *et al.*, 129 studies were analyzed with a total of 40,790 patients and postmenopausal bleeding was found in approximately 90% of patients with endometrial cancer [7]. There is a close relationship between the amount of estrogen and progesterone secreted by the ovaries from puberty to menopause and the development of hyperplastic endometrium and endometrial cancer.

The risk is increased in postmenopausal women who have had endocrine disturbances in the premenopausal period (menstrual disorders, polycystic ovary syndrome, obesity, absence of term pregnancy, absence of lactation). The duration of progesterone deficiency is a major determinant of risk [36].

Transvaginal ultrasound and/or outpatient endometrial biopsy are most commonly used methods for initial endometrial evaluation. According to Goldstein, the risk of endometrial malignancy in women with postmenopausal bleeding and endometrial thickness ≤ 4 mm is about 1:917 and endometrial biopsy is not indicated here. If a biopsy is performed on all of these patients who have a very thin endometrium, tissue is often obtained that is insufficient for diagnosis [37].

Elsandabese and Greenwood conducted a study in patients with postmenopausal bleeding and in 82% of those with an endometrial thickness < 5 mm a sample was successfully taken by endometrial biopsy, but only in 27% of them the sample was adequate for analysis and this was not in correlation with the parity or size of the uterine cavity [38].

In a meta-analysis by Smith-Bindman *et al.*, analyzing 35 studies with 5,892 women with postmenopausal uterine bleeding, a sensitivity of 96% and a specificity of 53% for endometrial malignancy was found for an endometrial thickness threshold of ≥ 5 mm [39].

Hysteroscopy largely replaces ultrasonography in the diagnosis of the etiology of postmenopausal bleeding and shows greater efficiency in the diagnosis of focal pathological changes that are difficult to detect on ultrasound [40].

The interpretation of endometrial thickness in perimenopausal women depends on the period of menstrual cycle when the ultrasound examination is performed. The most accurate results are obtained if the ultrasound is done from the fourth to the seventh day of the menstrual cycle, when menstruation is over [41].

Endometrial thickness less than 6 mm is commonly considered as non-hyperplastic [42]. There are cases when transvaginal ultrasound cannot distinguish endometrial hyperplasia from polyp because both conditions cause thickening of the endometrium [43].

In our study, the mean value of endometrial thickness was 7.9 mm in the functional changes group and 13.6 mm in the organic changes group, with a difference of 5.7 mm that was statistically significant ($p < 0.0001$). The mean endometrial thickness was 13.6 mm in perimenopausal and 10 mm in postmenopausal patients.

The difference of 3.6 mm was confirmed as a statistically significant. Perimenopausal patients had a significantly longer duration of uterine bleeding than postmenopausal patients (median 10 vs. 3.5 days; $p = 0.0009$) and significantly more intensive bleeding than patients in postmenopause.

In our study, organic endometrial changes were more prevalent than functional ones. They were present in 73.3% of perimenopausal and in 68.3% of postmenopausal women. Serna Torrijos *et al.* examined the histopathological findings of 779 postmenopausal patients who underwent endometrial sampling by hysteroscopy, aspiration biopsy or curettage and found functional changes in 42.5% of women, benign changes (polyp, myoma) in 3% of them, endometrial hyperplasia without atypia in 8.3%, endometrial hyperplasia with atypia in 1.4% and adenocarcinoma in 8.5% of women [44].

In our study, endometrial atrophy, which we classified as a functional change, was present only in postmenopausal women (in 26.7%). In the study by Milosevic *et al.*, endometrial atrophy was found in 32.7% of postmenopausal and in none of premenopausal women [34].

Dysfunctional bleeding is most common during the perimenopausal period (menopausal transition). Bleeding from the proliferative endometrium may be due to an anovulatory cycle and bleeding from the secretory endometrium may be due to ovulatory dysfunction [45].

In our study, a histopathological finding of prolonged and inadequate estrogen activity was present in 20% of perimenopausal and in 5% of postmenopausal women. Deficient secretory phase was present only in perimenopausal patients (6.7%).

Conclusions

Fractionated explorative curettage is an effective method for accurate diagnosis of pathological changes of the endometrium in women with abnormal uterine bleeding or ultrasonographically detected abnormal endometrial findings.

The most common histopathological change was an endometrial polyp (in 45% of patients). Endometrial adenocarcinoma was present in 3% of perimenopausal and in 5% of postmenopausal patients. Dysfunctional uterine bleeding (inadequate and prolonged estrogenic action and deficient secretory phase) was present in 26.7% of perimenopausal patients.

The endometrium had a significantly greater thickness in women with organic changes than in those with functional changes.

The anteroposterior diameter of the uterus, the duration and intense of bleeding was greater in women with organic changes than in those with functional changes, but this difference was not significant.

Perimenopausal patients had a significantly longer duration of bleeding, more intensive bleeding, thicker endometrium and greater anteroposterior uterine diameter than postmenopausal patients.

References

1. Droegemueller W, Katz V. Diagnostic procedures. In: Stenchever MA, Droegemueller W, Herbst AL, Mishell DR, Jr, eds. *Comprehensive gynecology*. 4th ed. St. Louis: Mosby; 2001: 219-49.
2. Butler WJ. Normal and abnormal uterine bleeding. In: Rock JA, Jones HW, III, eds. *Te Linde's operative gynecology*. 9th ed. Philadelphia: Lippincott Williams & Wilkins; 2003: 457-81.
3. Caron C, Tetu B, Laberge P, et al. Endocervical involvement by endometrial carcinoma on fractional curettage: A clinicopathological study of 37 cases. *Mod Pathol* 1991; 4:644-7.
4. Spencer CP, Whitehead MI. Endometrial assessment re-visited. *Br J Obstet Gynecol* 1999; 106:623-632.
5. Dilation and Curettage. Standard of care. Available at: <https://standardofcare.com/dilation-and-curettage/>. Accessed on 08.04.2022.
6. What are the symptoms of menopause? Eunice Kennedy Shriver National Institute of Child Health and Human Development. Available at: <http://nichd.nih.gov/health/topics/menopause/conditioninfo/Pages/symptoms.aspx>. Accessed on: 08.04.2022.
7. Clarke MA, Long BJ, Del Mar Morillo A, et al. Association of Endometrial Cancer Risk With Postmenopausal Bleeding in Women: A Systematic Review and Meta-analysis. *JAMA Intern Med*. 2018;178(9):1210–22.
8. Pernick N. Dysfunctional uterine bleeding. PathologyOutlines.com website. Available at: <https://pathologyoutlines.com/topic/uterusdub.html>. Accessed on 08.04.2022.
9. Radiology Reference Article – Radiopaedia.org – Endometrial thickness. Available at: <http://radiopaedia.org/articles/endometrial-thickness>. Accessed on 08.04.2022.
10. Sheth S, Hamper UM, Kurman RJ. Thickened endometrium in the postmenopausal woman-sonographic-pathologic correlation. *Radiology* 1993; 187:135-9.
11. Goldschmit R, Katz Z, Blickstein I, et al. The accuracy of endometrial Pipelle sampling with and without sonographic measurement of endometrial thickness. *Obstet Gynecol* 1993; 82:727-730.

12. Ilic-Forko J. Hiperplazija endometrija. In: Corusic A, Babic D, Shamija M, Shobat H, editors. Ginekoloska onkologija. Medicinska Naklada Zagreb; 2005.p 225-228.
13. Kurman RJ CM, Herrington CS, et al. WHO Classification of Tumours of Female Reproductive Organs. Lyon: International Agency for Research on Cancer; 2014.
14. Setiawan VW, Yang HP, Pike MC, McCann SE et al. Type I and II endometrial cancers: have they different risk factors? *J Clin Oncol* 2013; 31: 2607-18.
15. Defining Cancer. National Cancer Institute. Available at: <http://www.cancer.gov/cancertopics/cancerlibrary/what-is-cancer>. Accessed on 09.04.2022
16. International Agency for Research on Cancer. World Cancer Report 2014. World Health Organization. Chapter 5.12.
17. Hoffman BL, Schorge JO, Schaffer JI, Halvorson LM, Bradshaw KD, Cunningham FG, eds. "Endometrial Cancer". Williams Gynecology (2nd ed.). McGraw-Hill. 2012; p. 817.
18. Стојовски М. Ендометријален канцер, Во: Антоvsка В. Стојовски М, Гинекологија учебник наменет за студенти по медицина, специјализанти по гинекологија и акушерство и специјалисти гинеколози-акушери. Скопје; 2016, стр: 796-805.
19. Castaneda N. Sonographic Presentation of Endometrial Carcinoma Stage I: A Case Study. *Journal of Diagnostic Medical Sonography* 2018, Vol. 34(4) 292–7.
20. Hileeto WF, Fadare O, Martel M, Zheng W. Age dependent association of endometrial polyps with increased risk of cancer involvement. *World J Surg Oncol* 2005;3(1):8.
21. Стојовски М. Бенигни лезии на горен дел од генитален тракт. Во: Антоvsка В. Стојовски М, Гинекологија учебник наменет за студенти по медицина, специјализанти по гинекологија и акушерство и специјалисти гинеколози-акушери. Скопје; 2016, стр: 771-84.
22. Goldstein SR, Monteagudo A, Popiolek D, et al. Evaluation of endometrial polyps. *Am J Obstet Gynecol* 2002;186(4):669-74
23. Reslova T, Tosner J, Resl M, et al. Endometrial polyps. A clinical study of 245 cases. *Arch Gynecol Obstet* 1999;262:133-9.
24. Lieng M, Istre O, Qvigstad E. Treatment of endometrial polyps: a systematic review. *Acta Obstet Gynecol Scand* 2010;89:992-1002.
25. Abdelazim IA, Aboeazz A, Abdulkareem AF. Pipelle endometrial sampling versus conventional dilatation & curettage in patients with abnormal uterine bleeding. *J Turkish German Gynecol Assoc.* 2013;14(1):1-5.
26. Demirkiran F, Yavuz E, Erenel H, et al. Which is the best technique for endometrial sampling? Aspiration (pipelle) versus dilatation and curettage (D&C). *Arch Gynecol Obstet.* 2012;286(5):1277-82.
27. Hwang WY, Suh DH, Kim K, et al. Aspiration biopsy versus dilatation and curettage for endometrial hyperplasia prior to hysterectomy. *Diagnostic Pathology* 2021; 16(1): 7
28. Sherman ME, Mazur MT, Kurman RJ. Benign diseases of the endometrium. In: Kurman RJ, editor. Blaustein's pathology of the female genital tract. New York: Springer-Verlag; 2002. п.421-6.
29. Yuksel S, Tuna G, Goksever Celik H, Salman S. Endometrial polyps: Is there prediction of spontaneous regression possible? *Obstet Gynecol Sci* 2021;64(1):114-21.
30. Fernandez-Parra J, Rodriguez Oliver A, Lopez Criado S, et al. Hysteroscopic evaluation of endometrial polyps. *Int J Gynaecol Obstet* 2006;95(2): 144-8.
31. Ferazzi E, Zupi E, Leone FP, et al. How often are endometrial polyps malignant in asymptomatic postmenopausal women? A multicenter study. *Am J Obstet Gynecol* 2009 Mar;200(3):235.e1-6.
32. Kurman RJ. Blaustein's pathology of the female genital tract, 5th edition. New York: Springer – Verlag; 2002.
33. Mazur MT, Kurman RJ. Diagnosis of endometrial biopsies and curettings. New York: Springer Science + Business Media; 2005
34. Milosevic J, Dzordzevic B, Tasic M. Uticaj menopausalnog statusa na ucestalost i patohistoloske karakteristike hiperplazije i carcinoma endometrijuma kod bolesnica sa nenormalnim uterusnim krvarenjem. *Acta Medica Medianae* 2008;47(2):33-7.

35. Albers JR, Hull SK, Wesley RM. Abnormal uterine bleeding. *Am Fam Physician* 2004 Apr 15;69(8):1915-26.
36. Schindler AE. Progesteron deficiency and endometrial cancer risk. *Maturitas* 2009; 62:334-7.
37. Goldstein SR. The role of transvaginal ultrasound or endometrial biopsy in the evaluation of the menopausal endometrium. *Am J Obstet Gynecol.* 2009;201:5-11.
38. Elsandabesee D, Greenwood P. The performance of Pipelle endometrial sampling in a dedicated postmenopausal bleeding clinic. *J Obstet Gynecol* 2005;25:32-4.
39. Smith-Bindman R, Kerlikowske K, Feldstein VA, et al. Endovaginal ultrasound to exclude endometrial cancer and other endometrial abnormalities. *J Am Med Assoc.* 1998;280:1510-7.
40. Tinelli R, Tinelli FG, Cicinelli E, et al. The role of hysteroscopy with eye-directed biopsy in postmenopausal women with uterine bleeding and endometrial atrophy. *Menopause* 2008 Jul-Aug;15(4Pt1):737-42.
41. Abnormal vaginal bleeding in pre- and peri-menopausal women. A diagnostic guide for General Practitioners and Gynaecologists. Available at: [http://canceraustralia.gov.au/sites/default/files/publications/ncgc-vaginal-bleeding-flowcharts-march-20111_504af02038614.pdf]. Accessed on 09.04.2022.
42. Smith P, Bakos O, Heimer G, Ulmsten U. Transvaginal ultrasound for identifying endometrial abnormality. *Acta Obstet Gynecol Scand.* 1991;70:591-4.
43. Kupfer MC, Schiller VL, Hansen GC, Tessler FN. Transvaginal sonographic evaluation of endometrial polyps. *J Ultrasound Med.* 1994;13:535-9.
44. Serna Torrijos MC, de Merlo GG, Gonzalez Mirasol E, et al. Endometrial study in patients with postmenopausal metrorrhagia. *Arch Med Sci* 2016; 12(3):597-602.
45. Doraiswami S, Johnson T, Rao S, et al. Study of endometrial pathology in abnormal uterine bleeding. *J Obstet Gynaecol India.* 2011 Aug; 61(4):426-30.