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ENDOMETRIAL CARCINOMA IN ASYMPTOMATIC POSTMENOPAUSAL WOMEN WITH A THICKENED ENDOMETRIUM

KARCINOM ENDOMETRIJUMA KOD ŽENA U POSTMENOPAUZI, BEZ SIMPTOMA, SA ZADEBLJALIM ENDOMETRIJUMOM

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Summary

Introduction. The most common clinical manifestation of endometrial cancer is postmenopausal bleeding, as well as irregular uterine bleeding. Far less often, endometrial cancer may also be present in postmenopausal women without bleeding. The aim of our study was to examine the incidence of endometrial cancer in asymptomatic postmenopausal women with a thickened endometrium. **Material and Methods.** The research included 251 asymptomatic postmenopausal women with endometrial thickness over 4 mm established by ultrasound. Exploratory curettage was performed in all the patients, followed by histopathological examination of the obtained material. **Results**. The average age of the respondents was 65.38 ± 26.69 years. The average thickness of the endometrium was 15.68 ± 5.06 mm. Of all the patients, 70.13% presented with benign endometrial disease; endometrial polyps were found in 58.18% and simplex hyperplasia of the endometrium without atypia in 11.95%. Endometrial cancer was found in 1.59% of patients, ovarian cancer metastasis in 0.4%, and endometrial hyperplasia with atypia in 1.59% of patients. All cases of endometrial cancer were diagnosed in patients with endometrial thickness over 11 mm. **Conclusion.** The approach to asymptomatic women with endometrial hyperplasia should be individual. Exploratory curettage/hysteroscopy should be recommended to patients with endometrial thickness over 11 mm in order to detect and evaluate for endometrial cancer. Asymptomatic women with endometrial thickness of 4 - 10 mm should be further examined, especially in case of associated risk factors or other ultrasound parameters that indicate more serious endometrial pathology.

Key words: Endometrial Neoplasms; Postmenopause; Endometrial Hyperplasia; Ultrasonography; Risk Factors

Sažetak

Uvod. Najčešća klinička manifestacija karcinoma endometrijuma je krvarenje u postmenopauzi kao i iregularno krvarenje iz materice. Daleko ređe, karcinom endometrijuma može biti prisutan i kod žena u postmenopauzi koje ne krvare. Cilj našeg rada bio je da ispitamo učestalost karcinoma endometrijuma kod žena u postmenopauzi, bez simptoma, sa zadebljalim endometrijumom. **Materijal i metode.** Istraživanje je obuhvatilo 251 ženu bez simptoma, u postmenopauzi, sa ultrazvučno izmerenom debljinom endometrijuma većom od 4 mm. Svim ispitanicama je urađena eksplorativna kiretaža i načinjen patohistološki pregled dobijenog materijala. **Rezultati**. Prosečna starost ispitanica iznosila je 65,38 ±26,69 godina. Prosečna debljina endometrijuma iznosila je 15,68 ±5,06 mm. Benigno oboljenje endometrijuma imalo je 70,13% ispitanica: 58,18% polip endometrijuma, odnosno simpleks hiperplaziju endometrijuma bez atipije 11,95%. Kod 1,59% ispitanica utvrđeno je postojanje karcinoma endometrijuma, kod 0,4% ispitanica utvrdili smo prisustvo metastaze karcinoma jajnika, a kod 1,59% ispitanica utvrdili smo postojanje endometrijalne hiperplazije sa atipijom. Svi slučajevi karcinoma endometrijuma dijagnostikovani su kod pacijentkinja sa debljinom endometrijuma većom od 11 mm. **Zaključak.** Pristup ženama bez siptoma, sa hiperplazijom endometrijuma, treba da bude individualan. Pacijentkinjama sa debljinom endometrijuma većom od 11 mm treba preporučiti eksplorativnu kiretažu/histeroskopiju u cilju evaluacije na karcinom endometrijuma. Žene bez simptoma, sa debljinom endometrijuma 4–10 mm, uputiti na dalju dijagnostiku u slučaju prisustva faktora rizika kao i prisustva drugih ultrazvučnih parametara koji ukazuju na težu patologiju endometrijuma.

Ključne reči: neoplazme endometrijuma; postmenopauza; hiperplazija endometrijuma; ultrazvuk; faktori rizika

Introduction

Endometrial cancer is the most common malignant tumor of the female genital organs in developed countries [1]. In the last three decades, the incidence of endometrial cancer has increased by approximately 1% per year, which is primarily related to the increase in the proportion of obese and

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Abbreviations
US – ultrasound
ET – endometrial thickness
CIN – cervical intraepithelial neoplasia

elderly women [2, 3]. Also, in about 5% of cases, the occurrence of endometrial cancer is genetically determined by the mutation of one of the four mismatch repair genes [4]. Women with hereditary nonpolyposis colorectal cancer syndrome (Lynch syndrome) have a cumulative incidence of endometrial cancer of 20 - 60% by the age of 70 [4–6].

The most common clinical manifestation of endometrial cancer in postmenopausal women is uterine bleeding [7, 8]. However, endometrial cancer may also be found in postmenopausal women without bleeding, but with a thickened endometrium (endometrial hyperplasia) confirmed by a routine gynecological ultrasound examination [7]. The incidence of endometrial thickening in postmenopausal women is from 3% to 17%, while the incidence of postmenopausal endometrial cancer in asymptomatic women is up to 3% [9, 10].

The high rate of cure in the initial stages of the disease with about 80 - 85% five-year survival has created a false belief that endometrial cancer is a low-risk disease. Nonetheless, advanced stages of the disease, as well as some histological types of endometrial cancer, are associated with a poor prognosis [3]. Despite of this, modern guidelines for endometrial cancer do not recommend screening, or routine ultrasound (US) examination or endometrial biopsy in asymptomatic postmenopausal women, because they do not improve the outcome of endometrial cancer [11–15]. Screening for endometrial cancer is recommended only for women at risk for Lynch syndrome [15, 16].

The aim of this research was to examine the prevalence of endometrial cancer in asymptomatic postmenopausal women with a thickened endometrium in our sample and to try to answer the question if it is necessary to perform exploratory curettage/hysteroscopy in every patient with a thickened endometrium.

Material and Methods

The research was a retrospective study conducted at the Clinic of Gynecology and Obstetrics, Clinical Center of Vojvodina and it was approved by the Ethics Committee of the Clinical Center of Vojvodina. The research included 251 asymptomatic postmenopausal women who underwent fractional exploratory curettage due to a thickened endometrium in the period from January 1, 2020 to December 31, 2020. Exploratory curettage was performed under general intravenous anesthesia in the one-day hospital of the Department of General and Emergency Gynecology.

We defined postmenopausal women as those who have not had their period for more than a year. All women underwent a transvaginal US examination. As a criterion for a thickened endometrium, we used endometrial thickness (ET) ≥ 4 mm established by transvaginal ultrasound.

Histopathological analysis of the obtained material was done at the Center for Pathology and Histology, Faculty of Medicine, University of Novi Sad, and the final diagnosis was established. The patients waited 2 - 3 weeks for the histopathological findings. After data collection, a descriptive and univariate analysis was carried out. Data analysis was performed using the SPSS version 22 software.

Results

Out of a total of 342 postmenopausal patients who underwent fractional exploratory curettage in 2020, 251 patients were asymptomatic and included in further research. Due to postmenopausal bleeding, 91 patients were excluded from the study. The average age of the respondents was 65.38 ± 26.69 years. The average ET in the examined patients was 15.68 ± 5.06 mm.

The largest number of the respondents (70.13%) had a benign endometrial disease: endometrial polyps were found in 58.18% and simplex hyperplasia of the endometrium without atypia in 11.95%. Endometrial cancer was found in 1.59% of subjects, breast cancer metastases were found in 0.4%, and endometrial hyperplasia with atypia was found in 1.59% of patients **(Table 1)**.

All cases of endometrial cancer were diagnosed in patients with ET > 11 mm. Breast cancer metastasis was diagnosed in one patient with ET < 11 mm. Atypical endometrial hyperplasia was diagnosed in 2 patients (1.61%) with ET < 11 mm and in 2 patients (1.57%) with ET > 11 mm. The largest number of patients in both groups had endometrial polyps (56.7%, 59.68%) or endometrial hyperplasia without atypia (13.39%, 10.14%). Insufficient material was obtained in 22.83% of patients with ET > 11 mm and in 27.42% with ET < 11 mm **(Table 2)**.

Table 1. Histopathological findings of exploratory curettage
Tabela 1. *Patohistološki nalazi eksplorativne kiretaže*

	No./*Br.*	%
Endometrial cancer/*Karcinom endometrijuma*	4	1.59
Endometrial polyp/*Polip endometrijuma*	146	58.18
Simplex endometrial hyperplasia without atypia/*Simpleks hiperplazija bez atipije*	30	11.95
Simplex endometrial hyperplasia with atypia/*Simpleks hiperplazija sa atipijom*	4	1.59
Cervical cancer/*Karcinom grlića*	1	0.4
Cervical intraepithelial neoplasia 3/*Cervikalna intraepitelna neoplazija 3*	2	0.79
Breast cancer metastasis/*Metastaza karcinoma dojke*	1	0.4
Insufficient material/*Oskudan materijal*	63	25.1

Table 2. Histopathological diagnoses in relation to endometrial thickness
Tabela 2. *Patohistološke dijagnoze kod pacijentkinja prema debljini endometrijuma*

Endometrial thickness/*Debljina endometrijuma*	11 mm		< 11 mm		Total/*Ukupno*
	No./*Br.*	%	No./*Br.*	%	
Endometrial cancer/*Endometrijalni karcinom*	4	3.15	0	0	4
Endometrial polyp/*Endometrijalni polip*	72	56.7	72	59.68	146
Simplex endometrial hyperplasia without atypia/*Simpleks hiperplazija bez atipije*	17	13.39	13	10.48	30
Simplex endometrial hyperplasia with atypia/*Simpleks hiperplazija sa atipijom*	2	1.57	2	1.61	4
Cervical cancer/*Karcinom grlića*	1	0.79	0	0	1
Cervical intraepithelial neoplasia 3/*Cervikalna intraepitelna neoplazija 3*	2	1.57	0	0	2
Breast cancer metastasis/*Metastaza karcinoma dojke*	0	0	1	0.81	1
Insufficient material/*Oskudan materijal*	29	22.83	34	27.42	63
Total/*Ukupno*	127	50.60	124	49.40	251

Discussion

An increasing number of postmenopausal women without any gynecological symptoms have preventive gynecological examinations as well as transvaginal US examinations, even when it is not indicated, in order to detect ovarian tumors, uterine tumors or tumors of other organs of the small pelvis.

In case of accidental finding of thickened endometrium, the gynecologist immediately refers the patient to a tertiary health institution, for further examination, endometrial biopsy, i.e. exploratory curettage or hysteroscopy.

However, the accidental finding of a thickened endometrium in postmenopausal asymptomatic women is a diagnostic dilemma for gynecologists, because there are still no clear guidelines and consensus among gynecologists regarding the threshold value of ET when the patient should be referred for further diagnostics [5, 17]. Without clear guidelines, the incidental finding of a thickened endometrium is based on the clinician's decision, taking into account the patient's wishes and risk factors [17].

In case of postmenopausal women with bleeding, the guidelines are clear. A transvaginal US examination should be performed, and if the endometrium is > 4 mm, they should be referred for further diagnostics, since the probability of endometrial cancer increases with each increase in the thickness of the endometrium by 1 mm. If the thickness of the endometrium is between 8 - 11 mm, the probability increases by 1.17, whereas if the thickness is over 11 mm, the probability that it is endometrial cancer is 4.7 times higher [18]. If the thickness of the endometrium is < 4 mm, the risk of endometrial cancer is small, less than 1% (0.3%), and regular examination should be recommended, but if the woman has recurrent bleeding or continues to bleed, further invasive diagnostics should be performed [7, 19].

The ET > 4 or 5 mm, which is used as a cut off value in cases of postmenopausal bleeding, cannot be applied to asymptomatic postmenopausal women, due to poor positive predictive value. With this approach, asymptomatic women with a low risk of endometrial cancer are subjected to invasive diagnostics, which is associated with the risks of complications of the intervention itself, increase in stress and anxiety, without affecting the reduction of morbidity and mortality due to endometrial cancer [5, 11, 20].

In our research, endometrial cancer was diagnosed in 4 patients (1.59%), where all patients had an ET over 11 mm. Four patients (1.59%) were diagnosed with atypical endometrial hyperplasia, while 2 patients had ET under 11 mm and the other two over 11 mm. The largest number of patients had benign endometrial disease, namely endometrial polyps (58.18%) and endometrial hyperplasia without atypia (11.95%). Insufficient material was obtained from 25.1% of the respondents. Our results are consistent with those of other authors.

In their study of 148 asymptomatic postmenopausal patients with endometrial hyperplasia, Gambacciani et al. found one case of adenocarcinoma by hysteroscopic biopsy (0.7%) in a woman with ET was 16 mm. They found that transvaginal US, as a screening method for endometrial pathology in asymptomatic postmenopausal women, has 93.2% false positive results. They concluded that US measurement of ET in this population of women should not be recommended in order to detect endometrial cancer [21]. In their study of 81 asymptomatic postmenopausal women with thickened endometrium, Ghoubara et al. found endometrial carcinoma or atypical endometrial hyperplasia in only 4 women (4.9%), all of whom had ET ≥ 10 mm [22]. A study of Ozelci et al. included 148 asymptomatic postmenopausal women who underwent hysteroscopic biopsy of the endometrium, and endometrial cancer was found in only 0.7% (one) of the cases [23]. A study by Allam et al. in Egypt, in a similar population, determined the presence of atypical endometrial hyperplasia in 6.8% and endometrial cancer in 4.1% [24].

These wide variations may result from differences in study design, patients' demographics, the number of patients included in the study, as well as differences in ethnicity and profiles.

In 2018, Alcazar et al. published the first meta-analysis that compared the risk of endometrial cancer

in asymptomatic postmenopausal women with ET ≥ 11 mm versus < 11 mm. It was observed that the risk of endometrial cancer in women with ET ≥ 11 mm was almost three times higher than those with ET 5 - 10 mm [25].

A study by Smith et al. included 10.000 asymptomatic postmenopausal women and found that the risk of endometrial cancer in women with ET ≥ 11 mm was 6.7% with 100% sensitivity and 80% specificity for the detection of endometrial cancer, and this risk was similar to the risk of endometrial cancer in women with postmenopausal bleeding and ET ≥ 5 mm, which is 7.3%. They suggest that endometrial biopsy in asymptomatic postmenopausal women should be performed if the ET is ≥ 11 mm [26].

However, there are studies that failed to determine the threshold thickness of the endometrium in asymptomatic postmenopausal women, which would be used in clinical practice to rationalize further diagnostics, indicating that every woman should be offered further diagnostics [7, 9].

Today, numerous authors agree that when setting indications for further diagnostics in asymptomatic postmenopausal women, in addition to measuring the thickness of the endometrium, other risk factors should also be taken into account, such as: obesity - body mass index > 25, high blood pressure, diabetes mellitus type 2, nulliparity, infertility, polycystic ovary syndrome, early menarche/late menopause, use of exogenous estrogen or estrogen-secreting tumors, and use of Tamoxifen [14, 20, 26–28].

In a retrospective study Aggarwal et al. studied asymptomatic postmenopausal women and ET of 10 mm was used as a cut off value. Endometrial cancer was detected in 1.2% of subjects and atypical hyperplasia in 2.4%. In subjects with ET < 10 mm, histopathological analysis showed no malignancy. Endometrial cancer was diagnosed in patients with ET ≥ 10 mm, and all of these cases had at least one risk factor for endometrial cancer. The authors recommended using ET ≥ 10 mm as a threshold value for endometrial biopsy or hysteroscopy in asymptomatic postmenopausal women. In asymptomatic women with ET of 4 - 10 mm, the decision on further examinations should be made individually, from case to case, taking into account risk factors as well as US characteristics of the endometrium [20].

Also, current recommendations regarding asymptomatic postmenopausal women with ET < 11 mm, apart from ET other US characteristics should be examined: uniformity and homogeneity of the endometrium, presence of cystic changes within the endometrium, echogenicity of the endometrium in relation to the myometrium, whether there is a clear border between the endometrium and myometrium and what that border is like (regular, irregular, interrupted or undefined), color and power Doppler parameters: no color, minimal color to prominent color. Blood vessels and increased vascularity must also be observed and described: the number of dominant blood vessels, whether they are branched, and nature of the flow through the blood vessels (dispersed or circular) [15, 20, 29–33].

Every asymptomatic postmenopausal woman with ET of 4 - 10 mm, risk factors, and US parameters indicating more severe endometrial pathology, should be offered further diagnostics [20]. Each woman should be explained the potential benefits of further diagnostics as well as the risks and possible limitations of further testing for endometrial cancer in order to make a clear decision on further treatment. Women with increased risk of endometrial cancer should be informed about the risks and symptoms of endometrial cancer and encouraged to report any unexpected vaginal bleeding [15].

Conclusion

The approach to asymptomatic women with endometrial hyperplasia should be individual. Patients with endometrial thickness > 11 mm should be advised to undergo exploratory curettage/hysteroscopy in order to evaluate for endometrial cancer. Asymptomatic women with endometrial thickness of 4 - 10 mm should be referred for further diagnostics individually, in case of associated risk factors, as well as other ultrasound parameters which indicate more severe pathology of the endometrium.

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