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Differences in endometrial carcinoma presentations and characteristics in pre- and postmenopausal women

Разлике у презентацији и карактеристикама карцинома ендометријума код пре- и постменопаузалних жена

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SUMMARY

Introduction/Objective Recently increasing number of premenopausal women is diagnosed with endometrial carcinomas. Study aimed to determine if routinely collected clinical and imaging parameters, implying on tumor characteristics, are different in pre- and postmenopausal endometrial carcinoma patients, enabling their appropriate preoperative evaluation.

Methods The study included all patients (n=209) operated due to endometrial carcinoma during three years. The diagnosis was based on histopathological findings of exploratory curettage. Medical history was taken for all patients and they were divided regarding menopausal status. On preoperative ultrasound scan endometrial echo pattern was established. Existence of myomas, adnexal masses, free fluid in the abdomen or uterine cavity were noted. Magnetic resonance imaging detected the presence of pelvic metastases and tumor spreading into the uterine cavity, myometrium, cervix and lymph nodes. Postoperatively, histopathological findings, tumor stage and grade were established.

Results The majority of women were postmenopausal and secundiparous. Significantly more patients were obese, especially postmenopausal (p=0.001). Most tumors were Endometrioid adenocarcinomas regardless of menopausal status. Irregular/abnormal bleeding (p=0.037), presence of ascites (p=0.010), obesity (p=0.046) and lower parity (p=0.016) correlated with postmenopausal status. Large exophytic endometrial carcinomas were predominant in younger patients (p=0.026). Endometrial carcinomas were significantly more often diagnosed in the II FIGO stage in premenopausal patients. There were no other significant differences (endometrial thickness, uterine homogenity, echogenity, tumor infiltration and spreading, histopathological type and grade) between pre- and postmenopausal endometrial carcinoma patients.

Conclusions Few differences between pre- and postmenopausal endometrial carcinoma patients existed and the most prominent were obesity, parity, irregular/abnormal bleeding and tumor growth into the cavity.

Keywords: endometrial carcinoma; menopausal status; BMI; irregular abnormal bleeding; preoperative evaluation; ultrasound scan and MRI

САЖЕТАК

Увод/Циљ У последње време карцином ендометријума се дијагностикује код све већег броја пременопаузалних жена. Циљ студије је био да се утврди да ли су рутински прикупљени клинички и „имиџинг" параметри, који могу да укажу на карактеристике тумора, различити код пре- и постменопаузалних пацијенткиња са карциномом ендометријума, што би омогућило њихову правилну преоперативну процену.

Материјал Студија је обухватила све пацијенткиње (n = 209) операисане због карцинома ендометријума током три године. Дијагноза је заснована на хистопатолошким налазима експлоративне киретаже. За све пацијенте узета је детаљна анамнеза, а пацијенткиње су подељене према њиховом менопаузалном статусу. На преоперативном ултразвучном прегледу одређен је „ехо образац" ендометријума. Регистровано је постојање миома, аднексалних маса, слободне течности у абдомену или у кавуму утеруса. Магнетном резонанцом детектовано је присуство метастаза у малој карлици и ширење тумора на кавум утеруса, миометријум, грлић и лимфне чворове. Постоперативно, одређени су хистопатолошки тип, стадијум и градус тумора.

Резултати Већина пацијенткиња су биле постменопаузалне и секундипаре. Значајно више пацијенткиња су биле гојазне, анрочито постменопаузалних (p = 0.001). Већина тумора су били ендометриоидни аденокарциноми без обзира на менопаузални статус. Нередовно/абнормално крварење (p = 0,037), присуство асцитеса (p = 0,010), гојазност (p = 0,046) и нижи паритет (p = 0,016) су били повезани са постменопаузалним статусом. Велики егзофитични карциноми ендометријума били су доминантан налаз код млађих пацијената (p = 0,026). Карцином ендометријума је значајно чешће дијагностикован у FIGO стадијуму II код пременопаузалних пацијенткиња. Није било других значајних разлика (дебљина ендометријума, хомогеност и ехогеност материце, туморска инфилтрација и ширење, хистопатолошки тип и градус) између пре- и постменопаузалних пацијенткиња са карциномом ендметријума.

Закључак Мале разлике су постојале између пре- и постменопаузалних пацијенткиња са ендометријалним карциномом, а најзначајније су биле гојазност, паритет, нередовно/абнормално крварење и раст тумора ка материчној шупљини.

Кључне речи: карцином ендометријума; менопаузални статус; BMI; ирегуларно крварење; преоперативна процена; ултразвучни преглед и MRI

INTRODUCTION

Endometrial carcinoma is one of the most common malignant tumors of the female genital system. It accounts for about 4% of all malignancies in women worldwide [1]. Typical symptoms are irregular/abnormal bleeding and pelvic pain [2]. So far established risk factors, such as obesity, impaired lipid and carbohydrate metabolism, infertility and low parity, late onset of menopause and anovulatory cycles, are related to hyperestrogenism [3, 4].

Occurrence of endometrial carcinoma increases with age and it usually arises in postmenopausal women. However, recently increasing number of younger premenopausal women are being diagnosed with endometrial carcinoma possibly due to an epidemic of obesity and physical inactivity even of young girls [1, 5].

The differential diagnosis of different pathological conditions on the base of secretory endometrium can be difficult [5]. Good preoperative discrimination between benignant and malignant endometrial proliferations is essential for appropriate therapeutic approach. In postmenopausal women vaginal bleeding and/or endometrial thickness measured by transvaginal ultrasonography above 5mm are considered to be very suspicious of endometrial carcinoma and present the indication for exploratory curettage [6]. However, currently there are no algorithms based on clinical, laboratory and imaging parameters for assessment of premenopausal women that may have endometrial carcinoma.

Moreover, ultrasonographic examination sometimes has low diagnostic reliability with numerous false positive findings [7]. Although the exact diagnosis is achieved by examination of endometrial tissue samples obtained on fractionated exploratory curettage or hysteroscopy with endometrial biopsy, detection of malignant invasion of the myometrium is usually diagnosed by histopathological analysis only after hysterectomy [8].

The study aim was to determine if routinely collected clinical and imaging parameters, implying on tumor characteristics (histopathological diagnose – HP, grade, stage), are different in pre- and postmenopausal women, enabling appropriate preoperative evaluation of different age group patients with endometrial carcinoma.

METHODS

The study included all patients who were operated in three years period (January 1st 2011 up to December 31st 2013) due to endometrial carcinoma. The initial diagnosis and the decision for operative treatment were based on histopathological findings of exploratory curettage that all patients had either due to irregular/abnormal bleeding or endometrial thichening registered by ultrasound on regular gynecological check-up. Upon admission for operation, the standard medical history (irregular/abnormal bleeding, age, parity, menopausal status and age of menopause, use of hormone replacement therapy – HRT or Tamoxifen, comorbidities like breast carcinoma, hypertension – HT, diabetes mellitus – DM, etc.) was taken for all patients and their BMI (Body Mass Index) was calculated. Preoperatively, all patients had a detailed trans-vaginal ultrasound (TVUS) scan with measurement of endometrial thickness. The homogenity and echogenity of uterine tissue were evaluated. Existence of myomas and adnexal masses were noted. The presence of free fluid in the abdomen (ascites) as well as in the uterine cavity was also registered. Furthermore, patients underwent the magnetic resonance imaging (MRI) of the pelvis. By analyzing MRI images we determined tumor spreading into the uterine cavity, the myometrium, the cervix and the lymph nodes as well as the presence of pelvic metastases. Postoperatively, histopathological findings (HP) of the tumor (type, grade and stage) were analyzed. Staging was performed according to the new FIGO (International Federation of Gynecologist and Obstetricians) classification. All women were divided regarding their menopausal status and obtained data were analyzed accordingly.

Upon admission to hospital all women gave informed consent to all diagnostic and therapeutic procedures required for this study as well as enrolment in the study sample. Study procedure was performed in accordance with the ethical standards and it was approved by the Clinics Ethics Committee.

For the statistical analysis we used methods of descriptive and analytical statistics (percentages, $\chi2$ test, Kruskal Wallis nonparametric ANOVA, Spearman correlation, Binary linear regression) and a computer program SPSS 20.

RESULTS

Study involved 209 women who were operated due to endometrial carcinoma at the Clinic for Obstetrics and Gynecology, Clinical Center of Serbia throughout a period of 3 years (2011 – 2013).

In the examined population we registered significantly more postmenopausal (168; 80.4%) than premenopausal (41; 19.6%) women with endometrial carcinomas (χ^2=77.172; p=0.001). The majority of patients (n=83; 39.71%) were in their sixties, with an average age of 63.41 +/- 9.92 years (min=36; max 85). The mean BMI of investigated patients was 28.70 +/- 5.42 (min=17; max=40.9; premenopausal BMI 28.97 +/- 6.66; postmenopausal BMI 28.63 +/- 5.1). Significantly more women were obese (BMI >25 kg/m^2), especially in the postmenopausal group. The majority of women of both groups had two births and no abortions (Table 1).

Significantly more patients neither had previously diagnosed breast carcinoma nor administered therapy for it. Only 9 women had ever used hormonal replacement therapy. Investigated patients mostly did not have other comorbidities, but hypertension was very frequent. Majority of patients had irregular/abnormal bleeding. This was especially prominent for postmenopausal women (Table 1).

The mean endometrial thickness on preoperative TVUS scan was 12.21 +/- 8.46mm (min=3mm; max=39mm; premenopausal 13.45 +/- 10.8; postmenopausal 11.91 +/- 7.79). Significantly more women had pathologically increased endometrial thickness regardless of menopausal status (Table 2). Most tumors had exophytic growth filling the uterine cavity. On TVUS scan, significantly more both pre- and postmenopausal women had homogenous, but hyperechogenic endometrial presentation (Table 2). Significantly more women, regardless of their menopausal status, neither had TVUS findings of fluid in the uterus or abdomen, nor pelvic metastases, myomas or adnexal tumors on MRI. Myometrium was usually infiltrated less than 1/3 of its thickness in both investigated groups (Table 2).

Four different histopathological diagnoses of endometrial carcinomas were registered. The majority of tumors were Endometrioid adenocarcinomas regardless of menopausal status. Nevertheless, there were no cases of Carcinosarcoma and Clear cell carcinomas in premenopausal group. Majority of carcinomas in postmenopausal women were in FIGO stage I with grade G1, NG1, while in premenopausal group endometrial carcinomas were mostly registered in II stage and their predominant grade was G2, NG2 (Table 3).

Having irregular/abnormal bleeding, obesity and lower parity were significantly positively correlated with postmenopausal status. Ascites registered by MRI was significantly more frequent in postmenopausal women, while exophytic growth of endometrial carcinoma that filled out the uterine cavity was usually seen in younger patients. Moreover, FIGO stage was more advanced in premenopausal women. There were no other significant correlations or differences in examined parameters between pre- and postmenopausal endometrial carcinoma patients (Table 4).

A significant equation was constructed that shows which clinical, TVUS and MRI parameters assessed together can be used for differentiation between pre- and postmenopausal women with endometrial carcinoma (B=1.410; Wald=65.558; Exp(B)=4.098; R^2 Nagelkerke= 0.252; total classification=67.3%; χ^2=36.015; p=0.011). According to the obtained model the strongest differences are in irregular/abnormal bleeding (p=0.023), parity (p=0.004) and tumor growth into the cavity (p=0.035).

DISCUSSION

Endometrial carcinoma is usually registered in women older than 60 years [9]. This finding is consistent with our study, in which the average age of patients was 63 years. Still, the youngest patient was only 36 years old.

In some reports older age, tumor grade, involvement of the lower uterine segment and lymphovascular infiltration were proven as significant predictive factors of endometrial malignancy, influencing also the patient's survival [9]. Studies also confirmed that myometrial invasion, tumor diameter, cervical stromal invasion and lymphovascular space invasion were the most important parameters for preoperative evaluation and therapy type determination in patients with endometrial malignancies [10].

According to the literature data only few studies have evaluated the influence of risk factors for endometrial carcinoma in women of different ages (younger – premenopausal and older – postmenopausal). Early menarche and nulliparity were correlated with increased endometrial carcinoma risk in premenopausal, but not in the postmenopausal women in some investigations. Late menopause showed a stronger association with endometrial carcinoma in older (over 65 years) than in premenopausal patients [11, 12]. Parity in the population we

tested was found to be a significant predictive factor for malignancy only in postmenopausal women.

Women with elevated endogenous estrogen levels have an increased risk of endometrial carcinoma. The diagnosis of polycystic ovarian syndrome has been made in up to 30% of cases with endometrial carcinoma in selected groups of premenopausal women [12]. Obesity was confirmed through numerous studies as the main risk factor for endometrial carcinoma [11, 12]. Some authors suggest that this association is consistent only for postmenopausal women, while others confirmed correlation in premenopausal women as well [12]. In obesity, there is an increased level of free estrogen due to increased conversion of fatty tissues from androstenedione. Estrogen leads to chronic proliferation of endometrial cells, increasing the risk of carcinoma occurrence [13, 14]. In our population 75% of patients were obese (BMI>25), indicating that being overweight raises the risk of endometrial malignancy. Still, the obesity was proven as endometrial carcinoma risk factor only for postmenopausal patients.

Although the histopathological assessment of the endometrial biopsy remains the gold standard, TVUS is considered as the first step in any woman presenting with abnormal uterine bleeding [15]. A thin and regular endometrial line that is clearly visualized throughout the uterus is associated with a very low risk of endometrial carcinoma. Some authors believe that if endometrium is thinner than 5mm measured by TVUS even with postmenopausal bleeding a risk for carcinoma is low, but not ruled out, especially in case of persistent bleeding [16]. The value of TVUS in symptomatic premenopausal women and those using hormone substitution therapy is lower because the endometrial thickness regularly varies with changes of hormones during cycle. The data we obtained confirm previous findings which have shown that endometrial thickness above 5mm in women with postmenopausal bleeding can be considered as accurate diagnostic parameter of endometrial malignancy [6]. However, there were no significant differences in endometrial thickness of pre- and postmenopausal women with endometrial carcinoma.

MRI is an important imaging modality in the preoperative assessment of endometrial carcinoma patients providing valuable data regarding lesion location and qualitative information for preoperative staging [17, 18]. MRI is able to accurately predict (sensitivity and specificity above 85%) cervical involvement in endometrial carcinoma patients and allows making an adequate treatment decision [17, 19]. Some authors believe that reliability

of MRI is better in the postmenopausal than premenopausal women [18]. MRI findings in our population were mostly similar (echogenity, homogeneity, endometrial thickness, level of cervical and myometrial invasion at the time of diagnose, etc.) between pre- and postmenopausal women.

According to some available literature data, tumor volume influences the rate of endometrial carcinoma progression [20]. Based on our results the size of tumor within the uterine cavity measured by MRI (filling the whole cavity) was confirmed to be relevant parameter in premenopausal patients.

Some researchers have shown that positive peritoneal fluid cytology represents a marker for shorter time to recurrence of the disease and decreased survival rate of patients with endometrial carcinoma [21]. In the study population, only few patients had ascites and enlargement of lymph nodes. Nevertheless, free fluid in the abdominal cavity seen by MRI was registered more often in postmenopausal women.

Even though in the overall tested population the majority of carcinomas were diagnosed in early stages, numerous carcinomas in premenopausal patients were at the II FIGO stage at the time of diagnose. This might be due to the fact that irregular/abnormal bleeding in younger women is occasionally misdiagnosed and inappropriately treated.

CONCLUSION

In conclusion we confirmed that endometrial carcinoma is significantly more frequent in postmenopausal than premenopausal women, while Endometrioid adenocarcinoma is the most frequent histopathological diagnose regardless of menopausal status. There are few differences in endometrial carcinoma presentation/characteristics between pre- and postmenopausal patients. The presence of ascites was more frequent in postmenopausal women, while large exophytic endometrial carcinomas were predominant in younger patients. Endometrial thickness, uterine homogenity, echogenity, tumor infiltration and spreading at the time of diagnose were similar between pre- and postmenopausal women with endometrial carcinomas. Although most women had BMI>25, obesity presents endometrial carcinoma risk factor for postmenopausal patients. Postmenopausal bleeding enables establishing a diagnose at earlier stages, than irregular/abnormal bleeding in premenopausal patients.

Ultrasound and MRI are appropriate diagnostic tools in patients with endometrial carcinoma, but not their findings are not reliable for predicting tumor stage, grade or exact histopathological diagnose.

Conflict of interest: None declared.

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Table 1. Frequency of assessed characteristics in pre- and postmenopausal women and the significance of differences between tested parameter categories in the group

Parameter	Category	Premenopausal women		Postmenopausal women		Total population	
		n	%	n	%	n	%
Body mass index	appropriate	15	36.6	37	22	52	24.9
	obesity	26	63.4	131	78.0	157	75.1
	p	0.086		0.001		0.001	
Irregular/abnormal bleeding	no	14	34.1	32	19	46	22
	yes	27	65.9	136	81.0	163	78
	p	0.042		0.001		0.001	
Parity	0	6	14.6	29	17.3	35	16.8
	1	15	36.6	40	23.8	55	26.3
	2	13	31.7	87	51.8	100	47.8
	3 and more	7	17.1	12	7.1	19	9.1
	p	0.125		0.001		0.001	
Breast carcinoma	no	38	92.7	157	93.5	195	93.3
	yes	3	7.3	11	6.5	14	6.7
	p	0.001		0.001		0.001	
Tamoxifen use	no	40	97.6	157	93.5	197	94.3
	yes	1	2.4	11	6.5	12	5.7
	p	0.001		0.001		0.001	
Hormonal substitution	no	36	87.8	164	97.6	200	95.7
	yes	5	12.2	4	2.4	9	4.3
	p	0.001		0.001		0.001	
Comorbidities	no	25	61	59	35.1	84	40.2
	HTA	8	19.5	73	43.5	81	38.8
	diabetes mellitus	1	2.4	6	3.6	7	3.3
	both HTA / DM or other	7	17.1	30	17.9	37	17.7
	p	0.001		0.001		0.001	

p – difference between categories of tested parameter in the group; HTA – hypertension; DM – diabetes mellitus

Table 2. Examined parameters of tumors in pre- and postmenopausal women and the significance of differences between tested parameter categories in the group

Parameter	Category	Premenopausal women		Postmenopausal women		Total population	
		n	%	n	%	n	%
Homogeneity on TVUS	no	13	31.7	75	44.6	88	42.1
	yes	28	68.3	93	55.4	121	57.9
	p	0.019		0.165		0.001	
Echogenity on TVUS	normal	16	39	74	44	90	43.1
	hyper	25	61	94	56	119	56.9
	p	0.160		0.123		0.001	
Endometrium on TVUS	≤5 mm	9	22	36	21.4	45	21.5
	>5 mm	32	78	132	78.6	164	78.5
	p	0.001		0.001		0.001	
IU fluid on TVUS	no	29	70.7	137	81.5	166	79.4
	yes	12	29.3	31	18.5	43	20.6
	p	0.008		0.001		0.001	
Myoma on TVUS	no	31	75.6	129	76.8	160	76.6
	yes	10	24.4	39	23.2	49	23.4
	p	0.001		0.001		0.001	
Adnexal tumor on TVUS	no	36	87.8	150	89.3	186	89
	yes	5	12.2	18	10.7	23	11
	p	0.001		0.001		0.001	
Ascites on TVUS	no	33	80.5	157	93.5	190	90.9
	yes	8	19.5	11	6.5	19	9.1
	p	0.001		0.001		0.001	
Uterine cavity MRI	without tumor	10	24.4	73	43.5	83	39.7
	filled with tumor	31	75.6	95	56.5	126	60.3
	p	0.001		0.001		0.001	
Cervix on MRI	benignant	28	68.3	115	68.5	143	68.4
	malignant cells	13	31.7	53	31.5	66	31.6
	p	0.019		0.001		0.001	
Lymph nodes on MRI	benignant	35	85.4	150	89.3	185	88.5
	malignant cells	6	14.6	18	10.7	24	11.5
	p	0.001		0.001		0.001	
MRI pelvic metastases	no	35	85.4	155	92.3	190	90.9
	yes	6	14.6	13	7.7	19	9.1
	p	0.001		0.001		0.001	
Myometrium infiltration on MRI	unaffected	4	9.8	13	7.7	17	8.1
	<1/3	23	56.1	105	62.5	128	61.2
	1/3–2/3	13	31.7	45	26.8	58	27.8
	whole	1	2.4	5	3.0	6	2.9
	p	0.001		0.001		0.001	

TVUS – transvaginal ultrasound; MRI – magnetic resonance imaging; IU – intrauterine

Table 3. Postoperative diagnoses of tumors in pre- and postmenopausal women and the significance of differences between tested parameter categories in the group

Parameter	Category	Premenopausal women		Postmenopausal women		Total population	
		n	%	n	%	n	%
Tumor grade	G1, NG1	17	41.5	75	44.6	92	44.0
	G1, NG2	21	51.2	63	37.5	84	40.2
	G2, NG1	2	4.9	17	10.1	19	9.1
	G2, NG2	1	2.4	10	6.0	11	5.3
	G2, NG3	0	0	3	1.8	3	1.4
	p	0.001		0.001		0.001	
FIGO stage	Ia	11	26.8	38	22.6	49	23.4
	Ib	4	9.8	36	21.4	40	19.1
	Ic	1	2.4	21	12.5	22	10.5
	IIa	14	34.1	30	17.9	44	21.1
	IIb	7	17.1	19	11.3	26	12.4
	IIIa	1	2.4	14	8.3	15	7.2
	IIIb	2	4.9	3	1.8	5	2.4
	IIIc	1	2.4	7	4.2	8	3.8
	p	0.001		0.001		0.001	
HP DG	Endometrioid adenocarcinoma	39	95.1	150	89.3	189	90.4
	Carcinosarcoma	0	0	5	3.0	5	2.4
	Adenosquamous carcinoma	2	4.9	8	4.8	10	4.8
	Clear cell carcinoma	0	0	5	3.0	5	2.4
	p	0.001		0.001		0.001	

HP DG – histopathological diagnosis; p – difference between categories of tested parameter in the group

Table 4. Correlations and differences between investigated parameters regarding the menopausal status (pre- and postmenopausal) of women with endometrial carcinoma

Parameters	Correlations		Differences	
	Spearman ρ	p	KW χ^2	p
Body mass index	0.111	0.046	0.026	0.871
Irregular/abnormal bleeding	0.145	0.037	4.356	0.037
Breast carcinoma	-0.012	0.861	0.031	0.860
Tamoxifen use	0.070	0.313	1.023	0.312
Comorbidities	0.158	0.023	5.165	0.023
Parity	-0.166	0.016	5.730	0.017
Endometrium mm TVUS	-0.026	0.704	0.145	0.703
Homogeneity on TVUS	-0.104	0.134	2.251	0.133
Echogenity on TVUS	-0.040	0.563	0.338	0.561
IU fluid on TVUS	-0.106	0.126	2.348	0.125
Myoma on TVUS	-0.011	0.874	0.025	0.874
Adnexal tumor on TVUS	-0.019	0.787	0.073	0.786
Pelvic metastases	-0.095	0.170	1.887	0.170
Ascites on TVUS	0.179	0.009	6.671	0.010
Growth in uterine cavity on MRI	-0.155	0.025	4.978	0.026
Cervix spreading on MRI	-0.001	0.984	0.000	0.984
Lymph nodes on MRI	-0.049	0.483	0.496	0.481
Myometrium on MRI	-0.019	0.789	0.072	0.789
Tumor grade	0.025	0.715	0.134	0.715
FIGO stages (I, II, III)	-0.038	0.581	6.607	0.037
HP DG	0.079	0.258	1.287	0.257

HP DG – histopathological diagnosis; TVUS – transvaginal ultrasound; MRI – magnetic resonance imaging; IU – intrauterine; HRT – hormone replacement therapy