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CORRELATION BETWEEN ENDOMETRIAL NEOVASCULARIZATION AND RISK OF ENDOMETRIAL MALIGNANCY IN POSTMENOPAUSAL WOMEN

ПОВРЗАНОСТ ПОМЕЃУ НЕОВАСКУЛАРИЗАЦИЈАТА НА ЕНДОМЕТРИУМОТ СО РИЗИКОТ ОД ПОЈАВА НА ЕНДОМЕТРИЈАЛЕН МАЛИГНИТЕТ КАЈ ПОСТМЕНОПАУЗАЛНИ ПАЦИЕНТКИ

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Abstract

Introduction. The period that starts one year after the last menstruation is called menopause and it is divided into early and late menopause.
Aim. To examine the correlation between endometrial neovascularization and the risk of endometrial malignancy in postmenopausal women.
Methods. This is a prospective clinical study involving 120 postmenopausal patients treated at the University Clinic for Gynecology and Obstetrics-Skopje, divided into two groups: control and examination. The control group included 40 postmenopausal patients, hospitalized and operated due to urogenital pathology. The examined group consisted of 80 patients divided into two subgroups –the group with uterine bleeding and the other one without uterine bleeding. According to the ultrasound verified thickness of the endometrium, the two subgroups were divided according to endometrial thickness into: the first group with endometrial thickness from 5-8 mm; the second from >8-11 mm and the third group above 11 mm. We made ultrasound examination by measuring the resistant index (Ri) of the endometrium in both groups of patients as well as in subgroups, which were also divided into other subgroups according to endometrial thickness.
Results. The probability of endometrial malignancy was significantly increased by 0.097 times in postmenopausal patients.
Conclusion. Doppler examination of endovascular neovascularization (Ri) is a significant predictor of endometrial malignancy ($p<0.05$). Women with endometrial Doppler Ri>0.42 were 0.097 [p=0.029, 95% CI=0.012-0.787] times less likely to have endometrial cancer than women with endometrial Doppler Ri≤0.42.

Keywords: postmenopause, neovascularization,

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endometrial malignancy

Апстракт

Вовед. периодот што започнува една година по последната менструација се нарекува менопауза и тој е поделен на рана и доцна менопауза.
Цел. да се испита корелацијата помеѓу ендометријална неоваскуларизација и ризикот од ендометријален малигнитет кај жени во постменопауза.
Методи. Ова е проспективна клиничка студија која вклучува 120 постменопаузални пациентки третирани на Универзитетската клиника за гинекологија и акушерство-Скопје, поделена во две групи: контролна и испитувана група. Контролната група вклучува 40 постменопаузални пациенти, хоспитализирани и оперирани поради урогенитална патологија. Испитуваната група се состоеше од 80 пациенти поделени во две подгрупи-групата со крварење на матката и другата без крварење на матката. Според ултразвук проверена дебелина на ендометриумот, двете подгрупи со и без крварење ги поделивме според дебелината на ендометриумот во: првата со дебелина на ендометриум од 5-8 мм; втората од >8-11мм и третата над 11мм. Направивме ултразвучен преглед со мерење на резистентниот индекс (Ri) на ендометриумот на обете групи на пациенти и исто така подгрупи кои исто така се поделени во други подгрупи според дебелината на ендометриумот како што е претходно споменато во текстот.
Резултати. Веројатноста за ендометријална малигност е значително зголемена за 0,097 пати кај пациентки во постменопауза.
Заклучок. Резистентниот индекс (Ri)-е значаен предиктор за ендометријална малигнитет ($p<0.05$). Кај пациентките со ендометријален Ri> 0,42 имаат 0,097 [p=0,029, 95% CI=0,012-0,787] пати со помала веројатност да имаат ендометријален малигнитет во споредба со пацинтките кај кои е Ri≤0,42.

Клучни зборови: постменопауза, неоваскуларизација, ендометријална малигност

Introduction

The period one year after the last menstrual cycle is called menopause. In this period, a new source of estrogens is estrone. It is divided into early and late menopause. Late menopause, after 70 years, is called senile. In 10-15% of cases postmenopausal bleeding is caused by endometrial cancer, and usually abnormal uterine bleeding is caused by endometrial polyps or atrophy [1]. The incidence of endometrial cancer in postmenopausal patients is 0.7%, but it increases in patients with additional risk factors [2]. In this period, abnormal uterine bleeding belongs to polyps, endometrial atrophy, endometrial hyperplasia, endometrial carcinoma, submucosal fibroid, hormone therapy, uterine or uterine infections, use of certain drugs [3], etc.

According to the International Federation of Gynecology and Oncology (FIGO) the stages are subclassified into two pathological types. Type 1-estrogen-dependent [4] in which in 30-80% of cases the mutation of the PTEN gene is responsible for this type of malignant tumor. It occurs from complex atypical hyperplasia [5], it is associated with estrogen stimulation and is not aggressive [6]. Type 2-neurostrogen-dependent endometrial cancer is poorly differentiated, with a deep myometrial invasion, including lymph nodes, low progestin sensitivity and 58% five-year survival [7,8]. It develops from an atrophic endometrium and is not associated with hormone stimulation [6]; metastasizes and grows outside the uterine hull [6]. Mutations of the P53 gene occur in 50% of cases. Papillary serous mesonephroma belongs to this group. This neoplasm is very aggressive.

Aim

The purpose of the study was to investigate the predictive role by measuring the resistant index (Ri) of endometrial neovascularization in the onset of endometrial malignancy in postmenopausal patients.

Material and methods

This is a prospective clinical study involving 120 postmenopausal patients treated at the University Clinic for Gynecology and Obstetrics-Skopje, divided into two groups: control and examined. The control group included 40 postmenopausal patients, hospitalized and operated due to urogenital pathology. The examined group consisted of 80 patients divided into two subgroups-the group with uterine bleeding and the other one without uterine bleeding. According to the ultrasound verified thickness of the endometrium, the two subgroups were divided according to endometrial thickness into: the first group with endometrial thickness from 5-8 mm; the second from >8-11 mm and the third above 11 mm. We made ultrasound examination by measuring the resistant index (Ri) of the endometrium in both groups of patients as well as in subgroups, which were also divided into other subgroups according to endometrial thickness.

The study excluded patients in generative reproductive age, patients who were not able to do fractional exploratory curettage, patients with a personal history of malignant disease (past or current), patients with a personal anemia for benign or malignant tumors of the ovary, breast cancer patients treated with tamoxifen, patients with any pelvic surgery due to other gynecological pathology.

Statistical analysis

The data during the survey were analyzed with the statistical package SPSS 20.0. The Pearson Chi square homogeneity test was used to establish an association between certain attributive dichotomies of the two groups of respondents. The Shapiro-Wilk W test was used to determine the frequency distribution of certain variables. To test the significance of difference between two and more numerical variables with regular or irregular distribution of frequencies the Student's T-test for independent samples, the Mann Whitney U test and the Kruskal-Wallis ANOVA test were used. A significance level of $p < 0.05$ was used to determine the statistical significance.

Results

Descriptive analysis of the sample according to Doppler examination of endovascular neovascularization

Patients from both groups were analyzed according to the results of the Doppler examination of endovascular neovascularization (Ri), which is legal in all patients in the sample (Table 1). The mean Doppler level of endometrial neovascularization (Ri) in all patients was 0.1±0.2, with a minimum value of zero and a maximum value of 1. In the study group of patients, the average Doppler value of endometrial neovascularization (Ri) was 0.2±0.2, with a minimum value of zero and a maximum value of 1. In the control group, the mean Doppler value of endometrial neovascularization (Ri) was 0±0, with a minimum and maximum value of zero. According to the media analysis, 50% of patients surveyed/survived??, i.e. the control group had a Doppler value of endometrial neovascularization (Ri) higher than the consequent IQR = 0 (0-0.5) *vs.* IQR=0 (0-0). There was a significant difference between patients of the two groups ($p < 0.05$) in terms of the value

Table 1. Descriptive analysis in both groups and Doppler examination of endometrial neovascularization (Ri)

group	(Means)	number	(Std. Dev.)	minimum	maximum	mediana (IQR)

				(Min)	(Max)	
Examination	0.22	80	0.25	0	1	0 (0-0.5)
Control	0	40	0	0	0	0 (0-0)
Total value	0.15	120	0.23	0	1	0 (0-0.4)

Mann-Whitney U Test: Z=4.231 p=0.00004*, *significant for p<0.05

of Doppler examination of endometrial neovascularization (Ri) (Mann-Whitney U Test: Z=4.231 p=0.00004).

Analysis of the examined group according to endometrial thickness and Doppler examination of the endometrium (Ri)

Patients from the examined group were divided into three subgroups according to the thickness of the endometrium, and an analysis was made of the value of Doppler examination of endovascular neovascularization (Ri) in each of them (Table 2). In the first subgroup with an endometrial thickness of 5 to 8 mm, the mean Doppler value of endometrial neovascularization (Ri) was 0.2±0.2, with a minimum of zero and a maximum of 0.56. According to the media analysis, 50% of patients in this subgroup had a Doppler value of endometrial neovascularization (Ri) higher than IQR = 0.56 (0-0.45). In the second subgroup with endometrial thickness <8 mm-11 mm, the mean Doppler value of endometrial neovascularization (Ri) was 0.18±0.23, with a minimum value of zero and a maximum of 0.55. According to the median analysis, 50% of patients in this subgroup had a Doppler examination value of endometrial neovascularization (Ri) higher than IQR=0 (0-0.42). In the third subgroup with endometrial thickness <11 mm, the mean Doppler value of endometrial neovascularization (Ri) was 0.30±0.27, with a minimum value of zero and a maximum value of 1. According to media analysis, 50% of patients of this subgroup had a Doppler value of endometrial neovascularization (Ri) higher than IQR=0.4 (0-0.47). The tabular presentation of the descriptive analysis of the examined group by subgroups according to Doppler value of endometrial neovascularization is given in Table 2.

Table 2. Descriptive analysis of the examined group by thickness of endometrium and Doppler values of endometrium (Ri)

subgroups	(Means)	number	(Std. Dev.)	minimum (Min)	maximum (Max)	mediana (IQR)
5 – 8 mm	0.20	36	0.24	0	0.56	0 (0-0.45)
<8 – 11 mm	0.18	17	0.23	0	0.55	0 (0-0.42)
<11 mm	0.30	27	0.27	0	1	0.4 (0-0.47)
Total value	0.22	80	0.25	0	1	0 (0-0.5)

Kruskal-Wallis ANOVA: H=2.722 p=0.2564, *significant for p<0.05

Analysis of the examined group according to uterine bleeding and Doppler examination of endometrial neovascularization (Ri)

Within the examined group, additional analysis of the groups without/with uterine bleeding and Doppler examination of endometrial neovascularization was performed (Table 3). In the group without uterine bleeding, the mean Doppler value of endometrial neovascularization (Ri) was 0.23±0.23, with a minimum of zero and a maximum of 0.55. Fifty percentages of patients in this subgroup had a Doppler (Ri) examination of endometrial neovascularization higher than IQR=0 (0-0.46). In the group with uterine bleeding, the mean

Table 3. Descriptive analysis of the examined group with uterine bleeding and Doppler examination of endometrial neovascularization (Ri)

Uterine bleeding	(Means)	number	(Std. Dev.)	minimum (Min)	maximum (Max)	mediana (IQR)
No	0.23	40	0.23	0	0.55	0.19 (0-0.46)
Yes	0.23	40	0.27	0	1	0 (0-0.46)
Total amount	0.23	80	0.25	0	1	0 (0-0.46)

Mann-Whitney U Test: Z=-0.192 p=0.9846, *significant for p<0..05

Doppler value of endometrial neovascularization (Ri) was 0.23±0.27, with a minimum of zero and a maximum of 1. According to media analysis, 50% of patients had endometrial Doppler of IQR=0 (0-0.46). For p> 0.05, there was no statistically significant difference between the groups without / with uterine bleeding and Doppler examination of endometrial neovascularization (Ri) (Mann-Whitney U Test: Z =-0.1347 p=0.0893).

Analysis of groups without / with uterine bleeding according to endometrial thickness and Doppler examination of the endometrium (Ri)

An analysis of the group without uterine bleeding was performed according to endometrial thickness and endometrial Doppler (Ri) (Table 4). The analysis showed that the highest Doppler value of endometrial neovascularization (Ri) had the subgroup with endometrial thickness <11 mm, 0.33±0.23, followed by 0.21±0.23 in the subgroup with endometrial thickness <8 -11 mm and 0.19±0.24 in the endometrial thickness group of 5 to 8 mm. For p>0.05, there was no significant difference between the subgroups according to different endometrial thickness and Doppler values of endometrial neovascularization (Ri) (Kruskal-Wallis ANOVA test: H= 2.287, p=0.3187).

Table 4. Analysis of the group without uterine bleeding by thickness of endometrium and Doppler endometrial examination (Ri)

subgroups	(Means)	number	(Std. Dev.)	minimum (Min)	maximum (Max)	mediana (IQR)
5 - 8мм	0.19	19	0.24	0	0.55	0 (0-0.46)
<8 - 11мм	0.21	11	0.23	0	0.48	0 (0-0.42)
<11мм	0.33	10	0.23	0	0.56	0.4 (0-0.46)

An analysis of the group with uterine bleeding was performed according to endometrial thickness and Doppler values of endometrial neovascularization examination (Table 5). The analysis showed that the highest average level of Doppler examination of endometrial neovascularization (Ri) was in the subgroup with endometrial thickness <11 mm, 0.25±0.25, followed by 0.19±0.24 in the subgroup with endometrial thickness 5-8 mm and 0.14±0.22 in the endometrial thickness group <8-11 mm. For p>0.05, there was no significant difference between the subgroups according to different endometrial thickness and Doppler values of endometrial neovascularization (Ri) (Kruskal-Wallis ANOVA test: H=1.0796, p=0.5829).

Table 5. Analysis of the group with uterine bleeding according to the thickness of endometrium and Doppler examination of the endometrium (Ri)

subgroups	(Means)	number	(Std. Dev.)	minimum (Min)	maximum (Max)	mediana (IQR)
5 – 8 mm	0.19	17	0.24	0	0.56	0 (0-0.45)
<8 – 11 mm	0.17	6	0.26	0	0.55	0 (0-0.45)
<11 mm	0.28	17	0.30	0	1	0.4 (0-0.47)

Kruskal-Wallis ANOVA test: H=0.9472 p=0.6227, *significant for p<0.05

The predictive role of certain parameters in relation to the occurrence of endometrial malignancy in the subjects of the examined group was tested using binary logistic regression analysis.

Binary logistic regression analysis of the predictive role of certain parameters in relation to endometrial malignancy - examined group

Variable	B	S.E.	Wald	Df	Sig.	Exp(B)	95% C.I. for EXP(B)	
							Lower	Upper
Reference category Ri ≤ 0.42								
Ri >0.42	(2.335)	1.069	4.770	1	.029*	.097	.012	.787

* significant for p<0,05

Doppler examination of endometrial neovascularization (Ri) was a significant predictor of endometrial malignancy (p<0.05). Women with endometrial Ri> 0.42 were 0.097 [p=0.029, 95% CI=0.012-0.787] times less likely to have endometrial cancer than women without endometrial Ri≤0.42.

Discussion

Doppler examination of endovascular neovascularization (Ri) is a significant predictor of endometrial malignancy (p<0.05). Women with endometrial Doppler Ri>0.42 were 0.097 [p=0.029, 95% CI=0.012-0.787] times less likely to have endometrial cancer than women with endometrial Doppler Ri ≤ 0.42.

Alcazar *et al.* found a significantly lower resistance index in intratumoral tissues [9]. Kurjak and Kupeshik also found a low vascular resistance index (Ri=0.42. 0.02) in blood vessels in the central parts of the lesion as well as in the surrounding invasive myometrial blood vessels. They believe that they are the result of endothelial membrane deficiency [10]. Opolskiene *et al.* [11] examined the vascular model of endometrial malignancy, finding a low sensitivity of 80% and a specificity of 54% of power Doppler for endometrial malignancy.

Conclusion

The use of power Doppler as a secondary test in patients with postmenopausal bleeding is useful in marking/differentiating endometrial cancer from other causes of endometrial obesity. It can also be a promising screening tool in asymptomatic postmenopausal patients at risk for endometrial cancer.

Conflict of interest statement. None declared.

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