

Clinical and histopathological characteristics in patients with postmenopausal bleeding

Aljoša Mandić¹, Bojana Gutić¹, Tatjana Kapiclj-ković¹, Ljiljana Segedi Mladenović², Mihaela Mocko Kačanski²

SUMMARY

Background: Incidence of endometrial carcinoma in Vojvodina is 15-20/100 000. In 75% cases, endometrial carcinoma is diagnosed in postmenopausal period. In 90 % of patients, the first clinical sign is postmenopausal bleeding. The aim of the study was to investigate clinical and histopathological characteristics in patients with postmenopausal bleeding.

Methods: The study included 122 patients with postmenopausal bleeding. All of these patients underwent gynecological examination and vaginal ultrasound. We obtained materials for histopathological analysis by fractionate explorative curettage. Once we had definitive histopathological findings, we divided patients in two groups A (endometrial carcinoma) and B (benign changes).

Results: We confirmed significant statistical differences between examined group A and B, including age (64.49 compared with 58.81 years), postmenopausal period (13.67 instead 9.11 years), and length of uterine corpus (6.41 instead 5.25 cm).

Conclusion: Elderly women with longer postmenopausal interval and postmenopausal bleeding had increased risk for endometrial carcinoma. Measurement of endometrial thickness by transvaginal ultrasound appeared to be insufficient parameter for differentiating the benign from the malignant changes of endometrium. Patients with endometrial carcinoma had significantly longer corpus of uterus comparing to patients with benign changes. Body mass index was not found to be significant risk factor in development of endometrial carcinoma in the examined groups. Obesity was diagnosed in both groups, suggesting that increased body mass index is a risk factor for development of pathological changes in endometrium, which could lead to postmenopausal bleeding.

Key words: Endometrial Neoplasms; Postmenopause; Uterine Hemorrhage; Risk Factors; Ultrasonography; Curettage; Histological Techniques

INTRODUCTION

Postmenopausal bleeding (PMB) is vaginal bleeding in postmenopausal women, which is different from that we expect in women who use sequential hormonal substitution therapy (1).

Every postmenopausal bleeding, whether it is spot-like or heavy, requires further evaluation of these patients. It can be caused by benign changes in endometrial, which can be diffuse (hyperplasia and atrophy), focal (endometrial polyp), and malignant (2-4). Endometrial cancer represents 6% of all female cancers. In the U.S., Canada, and Western Europe endometrial cancer is diagnosed in 8% to 12% of all malignancies of women while in Eastern Europe it is diagnosed in 2% to 4% (5).

Cancer of uterine corpus is the sixth among cancers in women in the region of Vojvodina (6). Incidence of endometrial cancer depends on age. In women aged 40 years endometrial cancer occurs in 12/100 000, and in women aged 60 years it is 84/100 000 (7). Only 4% of these patients with endometrial cancer are women younger than 40 years, and 25% are women in premenopausal period. Approximately 75% of endometrial cancers occur in postmenopausal period, and 50% of these are associated with risk factors (7). Numerous multicentre epidemiological studies pointed to their existence and a high correlation between endometrial cancer and risk factors. There are endogenous and exogenous risk factors. Ninety percent of patients with endometrial cancer visit a gynecologist because of vaginal bleeding in the form of menometrorrhagia in perimenopause

or menstruation-like bleeding in postmenopause (8). Possibility that the postmenopausal bleeding is caused by endometrial cancer depends on patients age and it is diagnosed at approximately 9% of women 50 years old, 16% women 60 years old, 28% those of 70 years, and 60% at women of 80 years (9). Thus, it is necessary examine every PMB and find out the cause of it. Basic diagnostic approach considers (9):

- Anamnesis and gynecological examination
- Transvaginal ultrasound
- Methods of sampling endometrial tissue for histopathological analysis
- Additional diagnostic methods

MATERIAL AND METHODS

Our retrospective study included 122 patients in postmenopausal period that came to a gynecologist because of bleeding from uterus. We used data of patients who had their last period at least one year ago.

Basic clinical data were taken from the hospital records of the Oncology Institute of Vojvodina and Clinic for Gynecology and Obstetrics, Clinical Center of Vojvodina. After gynecological and examination by transvaginal ultrasound, the patients underwent fractionate explorative curettage in local or short-term intravenous anesthesia.

Histopathological analysis of the samples was done in the Department for pathology and cytological diagnostics, Oncology Institute of Vojvodina, and Center for pathology and histology, Clinical Center of Vojvodina.

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¹Oncology Institute of Vojvodina, Sremska Kamenica, Serbia, ²Clinical Center of Vojvodina, Novi Sad, Serbia

Correspondence to:

Dr. Aljoša Mandić, Oncology Institute of Vojvodina, Put doktra Goldmana 4, 21204 Sremska Kamenica, Serbia

mandic.aljosa@onk.ns.ac.rs

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Based on histopathological findings the patients were classified in two groups:

- Group A - patients with endometrial cancer
- Group B - absence of malignity, benign changes (hyperplasia of endometrium, myoma, endometrial polyp, atrophic endometrium).

Statistical processing

During statistical data processing, we calculated descriptive statistics – frequency, percent, mean values, and standard deviation. We presented our results using column charts, pie, histograms, and box-whiskers diagrams. We used t-test and analysis of variants for comparisons, to establish whether there was statistical significant difference between mean values numerical features. Significant differences ($p < 0.05$) were marked with *, and highly significant differences ($p < 0.01$) with **.

RESULTS

The study results were obtained after the analysis and statistical processing of hospital records of 122 patients. All patients were examined in the Oncology Institute of Vojvodina and Clinic for Gynecology and Obstetrics, Clinical Center of Vojvodina.

Average age of patients was 61.56 years. The youngest had 46 and the oldest had 88 years. The average weight and height of women was 79.20 kg and 162 cm, respectively. Average BMI was 30.23, which indicated obesity in the examined group with minimal BMI 18.03 and maximal 44.08. Average age of menarche was 13.56 years and average regular menstrual cycle was 28.76 days. Transvaginal ultrasound examination showed that average length of uterus was 5.81 cm (minimal length 3 cm and maximal length 12 cm). Average thickness of endometrium was 12.65 mm (minimal measured thickness was 4 mm and maximal was 50 mm). The average appearance of menopause was at 50.22 year and mean duration of menopause was 11.32 years (Table 1).

Table 1. Basic characteristics of patients for numeric variables

Numerical variables	Number of patients	Minimum	Maximum	Mean value	Standard deviation
Age of patient	122	46	88	61.56	8.83
Weight	122	45.00	120.00	79.20	13.86
Height	122	1.46	1.85	1.62	0.06
BMI	122	18.03	44.08	30.23	5.00
Menarche	122	10	17	13.56	1.53
Regularity of menstrual cycle	122	21	50	28.76	2.51
Length of corpus of uterus (cm)	122	3.00	12.00	5.81	1.73
Thickness of endometrium (mm)	122	4.00	50.00	12.66	6.95
Menopause	122	36	60	50.22	4.06
Years in menopause	122	0.5	48.00	11.32	9.66

Patients were divided in two groups based on histopathological findings obtained after fractionate explorative curettage.

Group A - patients with endometrial cancer

Group B - absence of malignity, benign changes (hyperplasia of endometrium, myoma, endometrial polyp, atrophic endometrium).

In A group, there were 59 patients and in group B 63 patients (Table 2).

Table 2. Patients

Group	Patients (No.)	Percent (%)
Malignant (A)	59	48.4
Benign (B)	63	51.6
Total	122	100.0

Endometroid type of adenocarcinoma was most frequently diagnosed in group A (78% patients). Adenoacanthoma was diagnosed in 3.4% of patients, as well as adenosquamous type. Clear cell tumor was detected in 6.7% cases and seropapillary type of adenocarcinoma was diagnosed in 6.8%. Mucinous type was diagnosed in 1.7% of patients in group A (Figure 1).

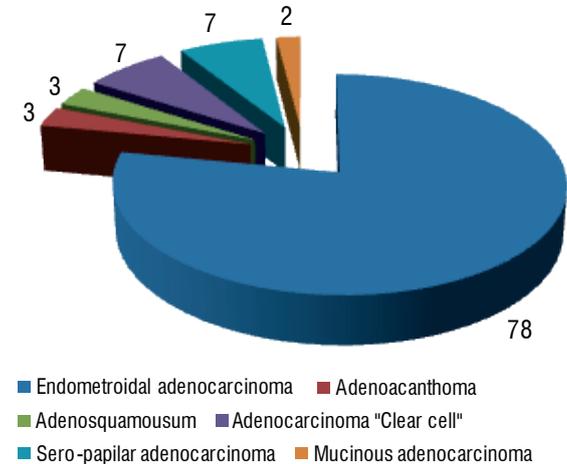


Figure 1. Histopathological findings in group A

According to differentiation degree of endometrial cancer, 35.6% of patients were well differentiated (G1), 45.8% were moderately differentiated (G2), and in 18.6% it was a poor differentiated tumor (Figure 2).

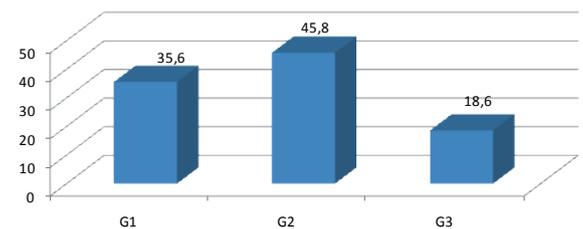


Figure 2. Differentiation degree of endometrial cancer tumor cells

Average age of patients with endometrial cancer was 64.49 years. The youngest patient had 50 years, and the oldest had 88 years. Average value of BMI was 30.55. Menarche averagely appeared at 13.51 year, and average regular cycle was 29.1 days. Transvaginal ultrasound examination showed that the average length of uterus corpus was 6.41 cm, and endometrial thickness was 13.36 mm (Table 3).

Histopathological findings in the B group showed that it is endometrial hyperplasia in 52.4%, in 25.4% it was diagnosed polyp, and in 19% atrophic endometrium, while submucous myoma was diagnosed in 3.2%. Submucous myoma was confirmed after hysterectomy (Figure 3).

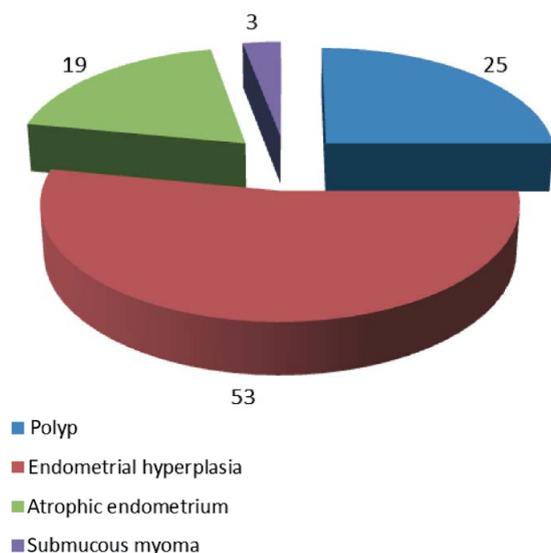


Figure 3. Histopathological findings in the B group

Average age of patients in the B group with benign changes was 58.81 years, the youngest was 46, and the oldest was 79 years old. Average weight was 78.73 kg, and height 162 cm. Average BMI was 29.92. Average time of menarche appearing in examined benign group was 13.6 year, and average regular cycle was 28.44 days. Transvaginal ultrasound examination measured the average length of uterus corpus was 5.25 cm, with minimal length 3 cm and maximal 10 cm. Average endometrial thickness was 11.99 mm (Table 3). Menopause appeared averagely in 50 year of life, and average duration of postmenopausal period was 9.11 years (Table 4).

We used t-test for equality of mean for testing of statistical significance between numerical variables of examined groups. Statistical significance was confirmed for age, length of uterus, and duration of menopause in both groups. Group of patients with malignant changes of endometrium was, on average, older (64.49 compared with 58.81 years); corpus of uterus was longer (6.41 compared with 5.25 cm), and their menopause lasted longer (13.67 compared to 9.11 years) (Table 5, Figures 4, 5 and 6). Other parameters had no significant statistical difference.

DISCUSSION

Endometrial cancer is most often diagnosed tumor of female genital tract in developed countries (9). In developing countries as well as it is in our country there is rising tendency for incidence of this cancer (10, 11). In 75% of cases, endometrial cancer appears in women in menopause so we can talk about cancer of older population. Incidence of endometrial cancer rises from 2/100 000 of women under 40 years old to 40-50/100 000 of women in sixth, seventh, and eight decade of life (12). Average age of women with endometrial cancer in our study was 64.49 years and that is a statistically significant difference from women with benign changes of endometrium with average age of 58.8 years. However, 25% of endometrial cancer appears in premenopausal period while 5% of diagnoses are established among women younger than 40 years (13). The risk for developing endometrial cancer is associated

Table 3. Basic characteristics of patients with malignant changes (Group A)

Numerical variables	Number of patients	Minimum	Maximum	Mean value	Standard deviation
Age of patient	59	50	88	64.49	8.80
Weight	59	52.00	120.00	79.71	12.90
Height	59	1.46	1.72	1.61	0.06
BMI	59	20.31	44.08	30.55	4.69
Menarche	59	10	17	13.51	1.60
Regularity of menstrual cycle	59	25	50	29.10	3.30
Length of corpus of uterus (cm)	59	4.00	12.00	6.41	1.91
Thickness of endometrium (mm)	59	5.00	50.00	13.36	7.50
Menopause	59	40	60	50.46	4.17
Years in menopause	59	0.5	48.00	13.67	10.15

Table 4. Basic characteristics of patients without malignant changes (Group B)

Numerical variables	Number of patients	Minimum	Maximum	Mean value	Standard deviation
Age of patient	63	46	79	58.81	7.99
Weight	63	45.00	120.00	78.73	14.80
Height	63	1.50	1.85	1.62	0.07
BMI	63	18.03	41.52	29.93	5.30
Menarche	63	11	17	13.60	1.47
Regularity of menstrual cycle	63	21	30	28.44	1.39
Length of corpus of uterus (cm)	63	3.00	10.00	5.25	1.33
Thickness of endometrium (mm)	63	4.00	36.00	11.99	6.38
Menopause	63	36	56	50.00	3.98
Years in menopause	63	0.5	35.0	9.11	8.69

Table 5. T-test for equality of mean in group A and group B

Numerical variables	T	Degree of freedom	Significance	Differences in mean
Age of patient	3.737	120	0.00**	5.68
Weight	0.390	120	0.698	0.9817
Height	-0.588	120	0.558	-0.0065133
BMI	0.688	120	0.493	0.6248
Menarche	-0.341	120	0.734	-0.0947
Regularity of menstrual cycle	1.450	120	0.150	0.66
Length of corpus of uterus (cm)	3.889	120	0.000**	1.1538
Thickness of endometrium (mm)	1.083	120	0.281	1.3626
Menopause	0.621	120	0.536	0.46
Years in menopause	2.670	120	0.009**	4.558

**significant statistical difference

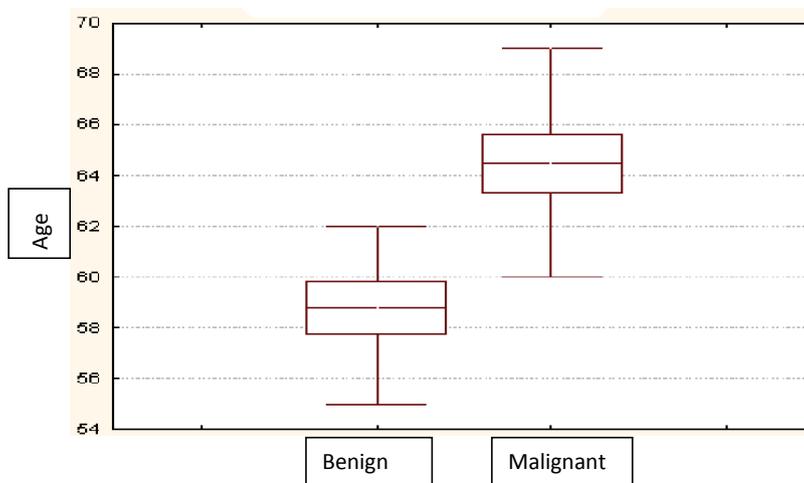


Figure 4. Box-whiskers relationship diagram of the display of the average age in the two groups

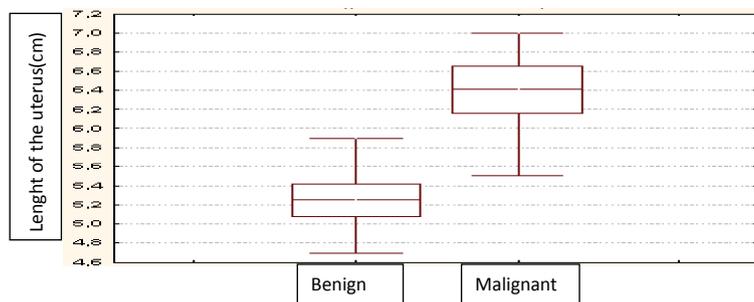


Figure 5. Box-whiskers relationship diagram of the display of the average length of uterus in the two groups

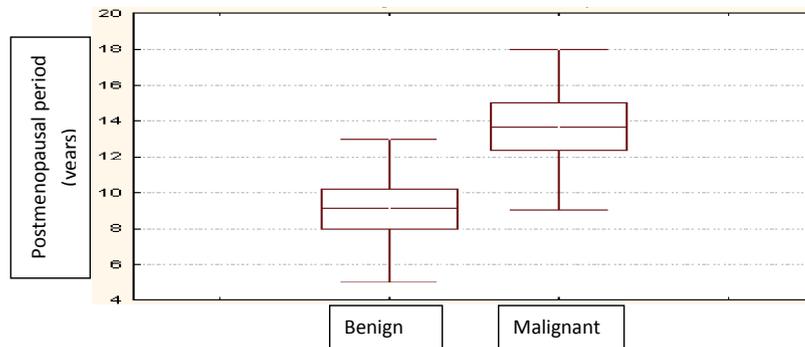


Figure 6. Box-whiskers relationship diagram of the display of the average duration of postmenopausal period in the two groups

with age of women. Therefore, longer postmenopausal period increases the risk for developing malignant change in endometrium (12). In our study, we confirmed statistically significant difference in length of postmenopausal period in women with malignant than in women with benign changes of endometrium.

Numerous studies report that obesity is important risk factor for developing of endometrial cancer (14-17). In our study, we did not confirm the difference in BMI between women with malignant and benign changes, since the total mean value for BMI for both groups is 30.32 and according to the classification of level of nutrition, all of them were obese. Based on that we can confirm that every endometrial change developed at the examined women, whether they are malignant or benign, depend of given risk factor, obesity.

Vermeulen, in his study, pointed to estrone as major estrogen for women in postmenopausal period, which is predominantly created by peripheral aromatization of circulating androstenedione (18). Incubation of adipose tissue in vitro using androstenedione and 19-hydroxysteroid as substrate showed conversion mostly to estrone. How is it going that production of estrone is associated with obesity degree, therefore stimulation of endometrium should be identical in both groups.

Among women in the postmenopausal period, bleeding from the genital organs is the main sign to visit a gynecologist. Malignant change and endometrial cancer also lead to postmenopausal bleeding. Although in 90% there is vaginal bleeding in endometrial cancer, cancer is cause of postmenopausal bleeding in 25% cases, so it is necessary to bear in mind other causes of bleeding from the genital organs. Gynecological examination is indispensable in order of distinguish the cause of

bleeding (1). Due to decreased production of estrogen after menopause, the appearance of the endometrium is changed and it becomes atrophic and on ultrasound examination, it appears as a thin line that represents stratum basale (19). Histological examination indicates that thickness of endometrium rarely exceeds 3 mm in physiological conditions. In addition, it is not possible to visualize endometrium in 7% to 10% of women in postmenopause that do not bleed from uterus (20). Numerous studies tried to define the threshold for thickness of endometrium by means of transvaginal ultrasound, which could indicate the existence of pathological changes in the endometrium. Smith-Bindman et al. make the meta-analysis of 35 studies and find that the sensitivity for detection of pathological changes on an endometrium is more than 92% if the endometrial thickness is 5 mm (21). A large multicentre study that included 1168 women with postmenopausal bleeding and the thickness of an endometrium 4 mm or less was conducted in Norway; of these women, Karlsson et al. diagnosed 14 who had pathological changes such as hyperplasia and polyp of endometrium. However, there was no cancer diagnosed. If we took this value as a threshold for appearance of pathological changes in an endometrium, the sensitivity would range from 96%, specificity 68%, PPV 61%, NPV 97%, and overall accuracy was 78%. When the threshold was 5 mm, sensitivity was 94%, specificity 78%, PPV 69%, NPV 96%, and overall accuracy was 84%. In an endometrium with thickness less than 5 mm, risk of appearance of pathological changes was 5.5% (22). Curcic established the threshold of endometrial thickness of 5 mm with sensitivity of 98%, specificity 44%, PPV 51%, NPV 98% for prediction of cancer and confirmed certainty for detection of endometrial cancer for this threshold (23).

In our study, average endometrial thickness of the examined women with postmenopausal bleeding was 12.66 mm. In the group with verified endometrial cancer, average endometrial thickness was 13.36 mm while it was 12 mm in the group with benign changes. Although there was obvious difference between average endometrial thicknesses, statistical significance was not confirmed. In addition, we did not determine that there was a significant difference in endometrial thickness regardless whether the change was malignant or benign. Curcic et al. confirmed significantly thicker endometrium in women with endometrial cancer concerning the women with benign changes (23). The same author established the statistical significance for the length of uterus in longitudinal section in women with malignancy with regard to benign group. In our study, we found that the length of uterus in longitudinal section was statistically different in patients with endometrial cancer compared to those with benign changes.

If we measured only the endometrial thickness in the both groups of patients, we would not be able to diagnose the real cause of PMB. The mean measurements of an endometrium are pathologic in the both groups, and all of these women were definitely indicated for histopathological analysis of the endometrium. The use of transvaginal ultrasound examination for diagnosis of pathological changes in endometrium is still the first diagnostic tool. Any thickness greater than 5 mm in the setting of postmenopausal bleeding or any endometrial heterogeneity or focal thickening seen at transvaginal US should be investigated. Therefore, there is no place to use it as a screening method in a general population. Langer et al. report that if the endometrial thickness is 5 mm or more, explorative curettage will be needed at half of those women, but only 10% of them would be diagnosed

as serious pathological endometrial change (24). Archer et al. diagnose one well-differentiated endometrial cancer of 801 asymptomatic postmenopausal women who have had substitution hormonal therapy (25). Gronroos et al. presented the results of screening among 597 high-risk women of age between 45 and 69 years who had hypertension and/or diabetes. No cancer was diagnosed, but 6 atypical hyperplasias were diagnosed (26).

Gupta et al. have analyzed 57 studies in their meta-analysis and they determine the most frequent limit values of endometrial thickness is from 4 to 5 mm; they also examined the accuracy of ultrasound as the only method in the detection of endometrial pathology. Their results indicate that the measurement of endometrium only has limits in prediction of hyperplasia or cancer, but it is very good test for excluding pathological changes of endometrium (27).

The problem in differential diagnosis of the PMB cause during standard vaginal ultrasound examination is to distinguish focal from diffuse changes and benign from malignant changes.

Today we use hysteroscopy and sonohysterography in distinguishing diffuse from focal changes (28-30).

Histopathological analysis of endometrial sample is the best method for establishing the diagnosis of endometrial cancer. Explorative curettage is not anymore a golden standard for getting the sample of endometrium; today, it is less invasive endometrial biopsy. If we use special aspirate biopsies (Pipelle or Vabrata) possibility for complications during explorative curettage are reduced. It is estimated that more than 50% curettages do not discover pathological changes of endometrium (31). Explorative curettage is associated with surgical complications including perforation in 0.6%-1.3%, bleeding in 0.4%, and infections in 0.3%-0.5% cases (32). Multiple studies show that the diagnostic curettage in diagnosis of irregular uterine bleeding is increasingly replaced by less invasive procedures such as endometrial biopsy or hysteroscopy, which are performed in outpatient conditions (30, 31, 33). In developed countries, curettage is a method of choice only if biopsy in outpatient facilities or direct hysteroscopy cannot be done. In the nowadays studies we can see that an endometrial biopsy is method of choice for diagnosis of premalignant and malignant endometrial condition; if there is focal endometrial lesion this method is not highly sensitive, unlike the hysteroscopy or sonohysterography (30-33).

CONCLUSION

Women with longer postmenopausal interval and PMB have higher risk for detection of endometrial cancer.

Endometrial thickness measured by transvaginal ultrasound is not sufficient parameter for differencing benign from malignant endometrial changes.

Patients with endometrial cancer have statistically significant longer uterine corpus than patients with benign endometrial changes.

Body mass index (BMI) was not a significant risk factor for endometrial cancer. In the both groups obesity is diagnosed which indicates BMI as a risk factor for developing of pathological changes in endometrium which could causes clinical symptom, PMB.

Conflict of interest

We declare no conflicts of interest.

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