Original article

INFLUENCE OF MENOPAUSAL STATUS ON FREQUENCY AND PATHOHISTOLOGICAL FEATURES OF ENDOMETRIAL HYPERPLASIA AND CARCINOMA IN PATIENTS WITH ABNORMAL UTERINE BLEEDING

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The aim of the study was to determine the frequency and pathohistological features of endometrial hyperplasia and carcinoma in premenopausal and postmenopausal patients with abnormal uterine bleeding (AUB).

The frequency and pathohistological features of endometrial hyperplasia and carcinoma were investigated in 961 patients with AUB who underwent dilatation and curettage (D&C) between January and December 2006. Regarding the menopausal status, patients were divided into two groups: group of premenopausal patients (n=808) and group of postmenopausal patients (n=153).

Endometrial hyperplasia was a significantly ($p<0,05$) more frequent cause of AUB in premenopausal patients (23,4%) than in postmenopausal patients (13,7%). AUB caused by endometrial carcinoma was significantly ($p<0,001$) more common in postmenopausal patients (18,9%) than in premenopausal patients (1,4%). Compared to the postmenopausal patients, endometrial hyperplasia without atypia was significantly ($p<0,01$) more frequent, while atypical hyperplasia was significantly ($p<0,05$) less frequent in premenopausal patients. In contrast to the premenopausal patients, endometrioid type and non-endometrioid type of endometrial carcinoma and carcinoma localized in endometrial polyp were significantly more common in postmenopausal patients ($p<0,001$, $p<0,001$, $p<0,05$, respectively).

Endometrial hyperplasia (diffuse or localized to the polyp) is more frequent cause of AUB in premenopausal patients than in postmenopausal patents. Compared to the premenopausal patients, atypical hyperplasia and endometrial carcinoma are more frequent causes of AUB in postmenopausal patients. In contrast to the premenopause, there were higher risks for developing endometrioid type and non-endometrioid type of endometrial carcinoma and carcinoma localized in endometrial polyp in postmenopause.
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Introduction

Menstrual bleeding is cyclic bleeding due to desquamation of secretory transformed endometrium, occurring at intervals of 28±7 days, and lasts average 3-5 days (1). Every bleeding which does not fulfill these criteria is abnormal uterine bleeding (AUB) (1). Regarding the age, except physiological uterine bleeding which can occur in newborns as a consequence of former exposure to mother's hormones, every bleeding before menarche is pathological. In reproductive period, AUB includes every variation in rhythm and character of bleeding (duration and intensity), as well as appearance of additional cyclic and acyclic (organic and dysfunctional) bleeding. Every bleeding from genital tract that occurs one year after menopause is abnormal bleeding.

Investigation of AUB is considerable providing that disturbances of menstrual cycle are the cause of 19,1% from the total of 20,1 millions of visits to the physicians, which is shown in one American national study (2). Also, AUB is the cause of 70% of visits to gynecological ordination in perimenopausal and postmenopausal period, and indication for 25% of gynecological operations (3,4).

Dilatation of uterine cervix and endometrial curettage are the most commonly used methods for obtaining endometrial sample, as well as its pathohistological evaluation. In new age, the precedence is given to conservative methods of examination of endometrium, i.e. minimally invasive

diagnostic procedures (transvaginal ultrasonography, hysteroscopy and endometrial biopsy) (5). However, there are investigations indicating that the routine endometrial curettage is yet the most reliable, and it is the method that can not be displaced in patients with uterine bleeding older than 40 years (6).

The main aims of the examination of patients with AUB are to exclude malignant tumors or hyperplasia of endometrium, and to precisely determine the etiology of bleeding with purpose to determine the optimal therapy for each patient (7).

The aim of this study was to determine the frequency and pathohistological features of endometrial hyperplasia and carcinoma in premenopausal and postmenopausal patients with abnormal uterine bleeding.

Methods

Retrospective investigation has been carried out in 961 patients with AUB who underwent dilatation of uterine cervix and endometrial curettage at the Clinic of Gynecology and Obstetrics in Nis between January and December 2006. Regarding the menopausal status, patients were divided into two groups: group of premenopausal patients (n=808) and group of postmenopausal patients (n=153).

All patents older than 45 years with period of amenorrhea lasting at least 12 months were classified as postmenopausal group, and the others were classified as postmenopausal group of patients.

Abnormal uterine bleeding is defined as every bleeding which does not correspond to menstrual bleeding or uterine bleeding one year after menopause.

Pathohistological analysis of endometrial samples fixed in 10% neutral formalin, routinely processed and stained with hematoxiline and eosine was performed at the Institute of Pathology, Faculty of Medicine in Nis.

Pathohistological findings in curettage specimens of patients with AUB were classified in eight groups: 1. changes related to gestation (retention of products of conception, endometritis, and gestational trophoblastic diseases); 2. proliferative endometrium; 3. secretory endometrium; 4. endometritis unrelated to gestation; 5. endometrial atrophy; 6. endometrial polyp; 7. endometrial hyperplasia; and 8. endometrial carcinoma.

Pathohistological classification of endometrial hyperplasia and carcinoma were done according to the criteria of the Word Health Organization (WHO) (8).

Statistical analysis was performed by using Excel 2000 and SPSS (Statistical Package for Social Sciences) 10,0. The results were presented as average, standard deviation, interval of variation (minimum-maximum) and index of structure (%). Fisher's exact test and Chi-square test were used for evaluation of significance of determined differences for attributive features. Differences were considered significant at $p<0,05$.

Results

Pathohistological findings in endometrial specimens were analyzed in 961 patients with AUB. All patients were aged between 18 and 83 (mean 43,23±6,7 years). With the aim to examine the etiology of AUB, 84,1% (808/961) of explorative endometrial curettage was performed in premenopausal patients and 15,9% (153/961) in postmenopausal patients.

Table 1 shows distribution of pathohistological findings in premenopausal and postmenopausal patients with AUB. Endometrial hyperplasia was significantly a more common cause of AUB ($p<0,05$) in premenopausal patients (23,4%) than in postmenopausal patients (13,7%). Uterine bleeding caused by endometrial carcinoma was significantly more frequent ($p<0,001$) in postmenopausal patents (18,9%) than in premenopausal patients (1,4%).

Table 1. Distribution of pathohistological findings in premenopausal and postmenopausal patients

Pathohistological finding	Premenopausal		Postmenopausal	
	n	%	n	%
Changes related to gestation	237	29,3	0	0,0
Endometritis	30	3,7	3	2,0
Proliferative endometrium	87	10,7	2	1,3
Secretory endometrium	130	16,1	0	0,0
Endometrial atrophy	0	0,0	48	31,4
Endometrial polyp	125	18,4	50	32,7
Endometrial hyperplasia	188*	23,4	21*	13,7
Endometrial carcinoma	11**	1,4	29**	18,9
Total	808	100,0	153	100,0

*p<0,05
**p<0,001

Pathohistological features of endometrial hyperplasia (type of hyperplasia and localization in polyp) in premenopausal and postmenopausal patients are shown in Table 2.

Table 2. Pathohistological features of endometrial hyperplasia in premenopausal and postmenopausal patients

Hyperplasia	Premenopausal		Postmenopausal		p
	n	%	n	%	
Without atypia					
Yes	181	22,4	16	10,5	p<0,01
No	627	77,6	137	89,5	
Atypical					
Yes	7	0,9	5	3,3	p<0,05
No	801	99,1	148	96,7	
Localized in polyp					
Yes	29	3,6	5	3,3	p>0,05
No	779	96,4	148	96,7	

Compared to the postmenopausal patients, higher frequency of hyperplasia without atypia is pathohistologically verified in postmenopausal patients (22,4% versus 10,5%). This difference was statistically significant (p<0,01). Atipical endometrial hyperplasia was more common in postmenopausal patients than in premenopausal patients (3,3% versus 0,9%). This difference was statistically significant (p<0,05). There was not statistically significant difference in frequency of endometrial hyperplasia localized in polyp between both examined groups (3,6% versus 3,3%) (p>0,05).

Table 3 shows pathohistological features of endometrial carcinoma (type of carcinoma and localization in polyp) in premenopausal and postmenopausal patients. Non-endometrioid type of endometrial carcinoma and carcinoma localized in endometrial polyp were registered only in postmenopausal patients. Compared to the premenopausal patients, endometrioid type and nonendometrioid type of endometrial carcinoma and carcinoma localized in endometrial polyp were significantly more common in postmenopausal patients (p<0,001, p<0,001, p<0,05, respectively).

Table 3. Pathohistological features of endometrial carcinoma in premenopausal and postmenopausal patients

Carcinoma	Premenopausal		Postmenopausal		p
	n	%	n	%	
Endometrioid					
Yes	11	1,4	20	13,1	p<0,001
No	797	98,6	133	86,9	
Non-endometrioid					
Yes	0	0,0	9	5,9	p<0,001
No	808	100,0	144	94,1	
Localized in polyp					
Yes	0	0,0	2	1,3	p<0,05
No	808	100,0	151	98,7	

Discussion

Determining the etiology of AUB, in respect to its frequency, is a very important problem in gynecology. Minimally invasive diagnostic procedures (transvaginal ultrasonography, hysteroscopy and endometrial biopsy) are of great value in the diagnosis of AUB, because they are simple, safe and acceptable for patients. However, some authors consider that the endoscopies are subjective and insufficiently sensitive for detecting endometrial lesions (7,9-15). According to the data, hysteroscopy is not more sensitive in detection of endometrial hyperplasia and carcinoma compared to the endometrial curettage (10). Of the total number of patients with pathohistologically confirmed endometrial hyperplasia and carcinoma, hyperplasia was hysteroscopically reported in 52% of patients and carcinoma was hysteroscopically registered in only 20% of patients (11). Examination of postmenopausal uterine bleeding by using transvaginal ultrasonography is compromised by the cases of endometrial carcinoma associated with thin endometrium (11-13). Evaluation of endometrial polyps by Color Doppler ultrasonography can not displace pathohistological evaluation of surgically removed polyps (24). Transvaginal sonohysteroscopy with the instillation of physiological solution is safe, noninvasive and inexpensive method applicable for selection of patients which require further pathohistological analysis (7,9,15).

According to the data, endometrial hyperplasia most frequently occurs in perimenopause as a consequence of anovulatory cycles (16,17). Although anovulatory cycles are common in the period following menarche, endometrial hyperplasia is not frequently diagnosed in adolescent patients because of AUB following menarche is rarely pathohistologically evaluated (16). In the reproductive period, endometrial hyperplasia is relatively rare and it predominantly occurs in obese women and women with polycystic ovarian disease (16). In postmenopausal patients, endometrial hyperplasia occurs as a result of unopposed exogenous or endogenous hyperestrogenism, i.e. as a consequence of exogenous estrogen therapy or conversion of androgens into estrogens in adipose tissue (16,17). Endometrial carcinoma occurs most frequently in postmenopausal women with the peak incidence in the sixth and the seventh decade of life (8,16,17). Only 1-8% of endometrial carcinoma occur before the age of 40 (16). In this study, it was determined that endometrial hyperplasia was significantly (p<0,05) more frequent cause of AUB in premenopausal patients than in postmenopausal patients. In contrast, AUB caused by endometrial carcinoma was significantly (p<0,001) more common in postmenopausal patients than in premenopausal patients. Compared to the postmenopausal patients, endometrial hyperplasia without atypia was significantly (p<0,01) more frequent while atypical hyperplasia was significantly (p<0,05) less frequent in premenopausal patients. There was no statistically significant difference in the frequency of endometrial hyperplasia localized in polyp between both examined groups. According to the data, older age and postmenopause increase the risk for developing atypical hyperplasia of endometrium and endometrial polyps with atypical hyperplasia (18,19).

There are two pathogenetic types of endometrial carcinoma, type I and type II. Type I carcinoma is estrogen-related or endometrioid type and represents about two-thirds of endometrial carcinoma (8,16,17). This carcinoma is usually well-differentiated, superficial, and responsive to the hormone therapy, and it has favorable prognosis (8,16). Pathohistologically, type I carcinoma is usually well- or moderately- differentiated endometrioid carcinoma of endome-trium (16,17). Type II carcinoma is non-estrogen related or non-endometrioid type and it occurs in older postmenopausal women in the absence of hyperestrogenism and endometrial hyperplasia. Non-endometrioid type of endometrial carcinoma is usually poorly differentiated, deeply invasive, and insensitive to hormone therapy, and it has unfavorable prognosis (16,17). Pathohistologically, type II carcinoma is usually serous or clear cell carcinoma of endometrium (16,17). The peaks of incidence are approximately 59 years for endometrial carcinoma

of endometrioid type and 68 years for endometrial carcinoma of non-endometrioid type (serous and clear cell) (8,16). In this study, endometrioid type and non-endometrioid type of endometrial carcinoma and carcinoma localized in endometrial polyp were significantly more frequent in premenopausal patients compared to the postmenopausal patients ($p<0,001$, $p<0,001$, $p<0,05$, respectively) which is in accordance with the data indicating that older age and postmenopause increase the risk for developing endometrial carcinoma and carcinoma localized in endometrial polyp (16-19).

Conclusion

Endometrial hyperplasia (diffuse or localized to the polyp) is a more frequent cause of AUB in premenopausal patients than in postmenopausal patents. Compared to the premenopausal patients, atypical hyperplasia and endometrial carcinoma are more frequent causes of AUB in postmenopausal patients. In contrast to the premenopause, there are higher risks for developing endometrioid type and non-endometrioid type of endometrial carcinoma and carcinoma localized in endometrial polyp in postmenopause.

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UTICAJ MENOPAUZALNOG STATUSA NA UČESTALOST I PATOHISTOLOŠKE KARAKTERISTIKE HIPERPLAZIJE I KARCINOMA ENDOMETRIJUMA KOD BOLESNICA SA NENORMALNIM UTERUSNIM KRVARENJEM

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Cilj rada bio je da utvrdi učestalost i patohistološke karakteristike hiperplazije i karcinoma endometrijuma kod bolesnica u premenopauzalnom i postmenopauzalnom periodu sa nenormalnim uterusnim krvarenjem (NUK).

Učestalost i patohistološke karakteristike hiperplazije i karcinoma endometrijuma ispitivane su kod 961 bolesnice sa NUK koje su bile podvrgnute dilataciji grlića materice i eksplorativnoj kiretaži endometrijuma u Klinici za ginekologiju i akušerstvo Kliničkog centra u Nišu u periodu od januara do decembara 2006. godine. U odnosu na menopauzalni status, sve bolesnice su podeljene u dve grupe, i to: grupa bolesnica u premenopauzi (n=808) i grupa u postmenopauzi (n=153).

Hiperplazija endometrijuma je statistički značajno češći uzrok NUK ($p<0,05$) kod bolesnica u premenopauzi (23,4%) u odnosu na bolesnice u postmenopauzi 3,7%). Krvarenje uslovljeno karcinomom endometrijuma je statistički signifikantno ($p<0,001$) češće kod bolesnica u postmenopauzi (18,9%) nego kod onih u premenopauzi (1,4%). U odnosu na bolesnice u postmenopauzi, kod bolesnica u premenopauzi signifikantno je češća hiperplazija bez atipije ($p<0,01$), a ređa atipična hiperplazija endometrijuma ($p<0,05$). Nasuprot bolesnicama u premenopauzi, kod bolesnica u postmenopauzi signifikantno su češći endometrioidni tip karcinoma endometrijuma ($p<0,001$), neendometrioidni tip karcinoma endometrijuma ($p<0,001$) i karcinom lokalizovan na polipu endometrijuma ($p<0,05$).

Hiperplazija endometrijuma (difuzna ili lokalizovana na polipu) je češći uzrok NUK kod bolesnica u premenopauzi nego kod u periodu postmenopauze. U poređenju sa bolesnicama premenopauzi, atipična hiperplazija i karcinom endometrijuma su češći uzrok NUK kod bolesnica u postmenopauzi. Nasuprot premenopauzalnom periodu, u postmenopauzalnom periodu života postoji veći rizik za nastanak endometrioidnog i neendometrioidnog tipa karcinoma endometrijuma i karcinoma lokalizovanog na polipu endometrijuma. *Acta Medica Medianae 2008;47(2):33-37.*

***Ključne reči**: menopauzalni status, endometrijum, hiperplazija, karcinom*