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ARTICLE

Effect of Hormone Replacement Therapy on Postmenopausal Endometrial Bleeding

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The aim of the study was to determine the effect of postmenopausal hormone replacement therapy (HRT) (treatment using estrogen only and sequential and continuous combined estrogen-progestogen treatment) on endometrial bleeding and histological changes of the endometrium. In a six-year period (2000-2005), 5893 patients were given care and the incidence of postmenopausal uterine bleeding was detected in groups of patients having and not having received hormonal treatment at the Menopause Outpatient Unit of the authors' department. In the case of bleeding, fractioned abrasion was performed and the samples were analyzed histologically. Among the postmenopausal patients who had not been given hormonal treatment, the incidence of bleeding episodes was significantly higher as among those having received hormonal treatment. In the samples, findings of proliferative endometrium occurred significantly more often in case of non-treated patients and those treated with sequential combined hormone therapy compared to patients receiving continuous combined hormone therapy. Although it was statistically not significant, hyperplasia simplex and complex together showed a tendency of reduced incidence in patients medicated by continuous combined treatment. These findings suggest that continuous combined hormonal treatment started at the right time (even before the menopause) may reduce the chances of the development of hyperplasia. A significantly higher incidence of hyperplasia was noted in patients using estrogen treatment only. It is possible that unopposed estrogen treatment further engraves an already diagnosed endometrial hyperplasia. In the group having received hormonal treatment, no complex hyperplasia accompanied by atypia occurred, only hyperplasia simplex was diagnosed in these cases. As a result of continuous reliance on combined preparations, the endometrium had become atrophied, therefore the chance of hyperplasia-related changes and of bleeding as a side effect decreased significantly. According to the authors' experience, hormonal treatment does not pose a risk to the development of endometrial carcinoma; on the contrary, continuous combined preparations appear to reduce the risk of hyperplasia and, indirectly, the chances of the development of adenocarcinoma. (Pathology Oncology Research Vol 13, No 4, 351–359)

Key words: climacterium, postmenopausal hormone therapy, menopause, irregular bleeding

Introduction

Menopause is the cessation of menstrual cycles which has already lasted for at least 12 months. That is why it is diagnosed retrospectively. Postmenopause comes after the cessation of climacteric symptoms, which may usually take place in 1-5 years. Perimenopause refers to the time preceding menopause.[33]

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The change in the quantity and frequency of bleeding during the menstrual periods, a major sign of premenopause, poses quite a challenge for many women. Usually, 10% of them experience immediate amenorrhea, 70% show symptoms of oligomenorrhea and/or hypomenorrhea, while 20% suffer from metrorrhagia and/or hypermenorrhea.[5,39] In addition to hormonal changes, menstrual irregularities in menopausal women are caused by benign and malignant changes of the genitals and, also, by systemic diseases. The risk of pregnancy should also be considered since ovulation may occur even in the menopause.[26,27,37,48]

It is essential to remember that irregular bleeding is the most frequent symptom of uterine cancer.[45] In post-

menopausal bleeding, carcinoma of the endometrium can be expected in 3-10% of the cases, and in 95% of endometrial carcinoma patients, previous bleeding from the uterus is detected.[3] Although endometrial carcinoma rarely occurs in young age, a steep rise in frequency is noted after 45 years of age.[12] Therefore, a biopsy of the endometrium for histological investigations is a must in menopausal women with irregular bleeding.[33]

Earlier, dilatation and curettage (D&C) were used as an established practice, while disposable flexible aspirators not requiring vacuum suction were developed in the early 1980s. Since then they have been used to replace D&C.[18,29] Taking biopsies of the endometrium on an outpatient basis has been a comfortable intervention; the sensitivity of diagnosing uterine cancer remained over 90%,[9,29] possible hidden focal changes being a drawback of the technique.[15]

With the spread of pelvic ultrasonography, many clinicians have thought that histological investigations can be substituted using vaginal ultrasonography to measure the thickness of the endometrium. If the endometrium is thinner than 8 mm, practically no form of hyperplasia has to be considered.[10] It may happen and yield false positive results when, in certain cases, the atrophied endometrium is measured to be thicker than it really is.[32]

In the period of the postmenopause, it is often a change of the endometrium that lies in the background of bleeding. According to control ultrasonographic tests, the incidence of an altered endometrium is found to be 41% and 28% for all women in the period of menopause and asymptomatic patients, respectively. Changes of the endometrium in postmenopausal women receiving hormone replacement therapy accompanied by irregular bleeding occur one and a half time more frequently than in those without irregularity, so bleeding often appears to be the first symptom of endometrial disease, however, its absence does not exclude the possibility of organic changes.[34] In more than half of the women receiving hormone replacement therapy, the endometrium is thicker than 8 mm according to ultrasonographic measurements, although a pathological change of the endometrium is found in only 4%. For this reason, and also because abnormal changes of the endometrium were found in cases when its thickness was below 2x4 mm, ultrasonography alone was not enough to reveal the condition of the endometrium in patients receiving hormone replacement therapy.[30] The accumulation of fluid in the uterine cavity is not necessarily suggestive of endometrial carcinoma.[38]

Sonohysterography performed using saline solution was found to be more effective.[4,16] In many departments, hysteroscopy, performed on an outpatient basis, has become a safe and effective technique of detecting irregular bleedings.[34,35] Recent observations appear to confirm that both hysteroscopy and sonohysterography may result in the spread of endometrial tumor cells, therefore they should be delayed until the histological results of endometrial biopsy have ruled out the presence of malignant changes.[31,50] As far as cost-effectiveness is regarded, a combination of ultrasonography and histological biopsy were found to be the cheapest solution.[7]

Since D&C can be performed in the frame of one-day hospitalization, this intervention is suitable for detecting focal endometrial changes and is not accompanied with the spread of tumor cells, let alone the therapeutic effect seen in many cases of irregular bleeding. In the case of irregular bleeding,

Table 1. **Hormone preparations selected for treating postmenopausal patients registered in our Menopause Outpatient Unit between 2000 and 2005**

Type of treatment	*Preparations*	*Treatment ceased*	*Presently treated*	*Total*
Estrogen	Dermestril	173	85	258
	Estraderm	90	11	101
	Estrimax	21	36	57
	Estrofem	184	69	253
Sequential combined treatment	Climen 28	1	0	1
	Trisequens	449	97	546
	Estracomb	116	44	160
	Femoston	8	16	24
Continuous combined treatment	Activelle	121	72	193
	Kliogest	193	19	212
	Livial	122	94	216
	Pausogest	38	31	69
	Estragest	15	17	32
No. of treated patients		1531	591	2122
No. of untreated patients				3771
Total no. of patients				5893

fractioned abrasion and the histological investigations of samples, obtained in two fractions, are done.[33] Therefore we have decided to study if it is possible to detect any histological differences among women receiving care for postmenopausal irregular bleeding, depending on whether they had been given hormone replacement therapy or not.

Patients and Methods

In the six-year period between January 1, 2000 and December 31, 2005, 5893 patients were given care at the Menopause Outpatient Unit of the 1st Department of Obstetrics and Gynecology at Semmelweis University. Among these women, 2122 patients (36%) have received hormone replacement therapy while 3771 of them (64%) did not rely on such treatment. Among the 5893 patients, 707 (12%) reported irregular bleeding. Of those bleeding, 577 women (81.6%) had not received hormone replacement treatment earlier; in 130 patients (18.4%), however, one or another form of hormonal treatment was applied, as part of their postmenopausal care.

Table 2. **Previous hormone replacement therapy of 130 patients registered at our unit because of bleeding disturbances**

Type of treatment	*Preparations*	*No. of cases*	*%*	
Estrogen	Estraderm	4	3.08%	3.85%
	Estrofem	1	0.77%	
Sequential combined treatment	Climen 28	1	0.77%	65.38%
	Estracomb	12	9.23%	
	Trisequens	72	55.38%	
Continuous combined treatment	Kliogest	39	30.00%	30.77%
	Pausogest	1	0.77%	
Total no. of patients	130	100.00%		

Table 3. **Age distribution of patients with bleeding disorders**

		Age of patients (years)	
	No. of patients	*Mean±SD*	*Median (range)*
Treated with hormones	130	56.5±5.7	56 (39-81)
Not treated with hormones	577	51.6±5.5	51 (37-71)
Total	707	54.7±6.1	54 (37-81)

The patients suffering from menstrual irregularity underwent fractioned curettage in which cervical and corporal scrapes were obtained for histological investigations.

Tables 1 and *2* summarize the medications used in hormone treatment. In our sample, of the 130 hormonally treated patients who had presented at our department for irregular bleeding, only 5 women (3.85%) were given estrogen only, 85 patients (65.38%) received sequential combined preparations, while 40 women (30.77%) took continuous combined preparations. (The estrogen-only treatments were not started at our department.)

The main aim of our study was to determine the effect of hormonal replacement therapy on the incidence of bleeding disorders and different types of histological results after fractionated curettage.

Data analysis was done by SPSS statistics software; $p<0.05$ was considered statistically significant. During the statistical analysis χ^2 test or χ^2 test with Yates correction and Student's t-test were used.

Results

The mean age of the 707 patients treated at our department for irregular bleeding was 54.7 years (*Table 3*). The difference between the mean ages of the treated and non-treated patients was tested using paired t-test; the patients who had not received hormone treatment turned out to be significantly younger ($p<0.0001$). Analyzing the age distribution of women according to menopausal status revealed that in the hormonally treated group most of the patients were in the postmenopausal stage (87%), while in the non-treated group the patients were rather in pre- and perimenopausal stage and only 20% of them were in postmenopause (*Table 4*). In the group not receiving hormonal treatment, the incidence of bleeding was significantly higher than in the treated group (577/3771, 15.3% vs. 130/2122, 6.1%, $p<0.001$).

Considering the above mentioned age distribution of patients in our statistical analysis we compared only the data of those patients who were in the postmenopausal stage. The histological findings of postmenopausal patients who underwent fractional abrasion for irregular bleeding are listed in *Tables 5* and *6*.

The incidence of atrophic endometrium was not significantly different between the groups. However, taking into consideration the histologically not evaluable and atrophic endometrium groups together, assuming that atrophic endometrium can cause both histological results, we found that these histological categories occurred significantly more often in the continuous hormonal therapy group than either in the non-treated or the sequential combined hormonal therapy group ($p=0.004$ and $p<0.001$, respectively). On the other hand, significantly less patients were found to be in the pro-

Table 4. **Distribution of patients according to menopausal status**

	Hormonal therapy	*No hormonal therapy*
All menopausal stages		
Patients with bleeding	130	577
Patients with no bleeding	1992	3194
Total	2122	3771
Postmenopausal women		
Patients with bleeding	120 (92.3%)	117 (20.3%)
(% of postmenopausal)	1834 (92.1%)	652 (20.4%)
Patients with no bleeding (% of postmenopausal)		
Total (% of postmenopausal)	1954 (92.1%)	769 (20.4%)

liferative stage in the continuous combined hormonal treatment group than either in the non-treated or the sequential combined medication group ($p<0.05$ and $p<0.01$, respectively; *Table 5*). Secreting mucous membranes were found significantly more often in the sequential combined hormonal therapy group than in the non-treated group ($p=0.03$). There were no cases of secreting mucous membrane in the group taking continuous combined medication.

Hyperplasia simplex were detected significantly more often in the estrogen-only treatment group than in the non-treated group $p=0.002$), while the other groups did not show any significant difference in this regard. Complex hyperplasia, in combination with signs of atypia and endometrial carcinoma were exclusively present among non-treated patients.

Other histological findings such as desquamation phase, hormonal dysfunction, chronic endometritis and endometrial polyp did not differ significantly between the compared groups.

Comparing the histological results of cervical scrapings it could be concluded that there was a significantly higher incidence of polyps both in the sequential and continuous combined treatment groups than in non-treated patients ($p=0.007$).

Those cervical scrapings that were histologically not evaluable occurred significantly more often in the non-treated group than in the sequential combined treatment one ($p=0.03$), in the continuous combined treatment group than in the non-treated one ($p=0.006$) and in the continuous combined vs. the sequential combined hormonal treatment group ($p<0.001$). Other cervical histological findings did not show any significant difference between the compared groups.

Discussion

Estrogens, initially used in the form of monotherapy, have been applied to relieve menopausal women's complaints since the 1940s. Although shortly after the appearance of postmenopausal hormone replacement therapy, a cause-and-effect relationship between estrogens and endometrial carcinoma was suspected, it could be proved in as late as 1974.[9]

Table 5. **Histological diagnosis of postmenopausal patients with bleeding disorders – results of fractionated curettage (endometrial mucosa)**

	Untreated (%)	*Estrogen (%)*	*Sequential combined (%)*	*Continuous combined (%)*	*Total*
Not evaluated	15 (12.8%)	1 (20%)	5 (6.5%9	16 (42.1%)	37
Atrophy	34 (29.1%)	0 (0%)	15 (19.5%)	10 (26.3%)	59
Not evaluated+ atrophy	49 (41.9%)	1 (20%)	20 (26.0%)	26 (68.4%)	96
Proliferation phase	34 (29.1%)	1 (20%)	28 (36.4%)	5 (13.2%)	68
Secretion signs	9 (7.7%)	0 (0%)	14 (18.2%)	0 (0%)	23
Desquamation phase	0 (0%)	0 (0%)	1 (1.3%)	0 (0%)	1
Hormonal dysfunction	0 (0.85%)	0 (0%)	1 (1.3%)	2 (5.3%)	4
Chronic endometritis	3 (2.6%)	0 (0%)	1 (1.3%)	0 (0%)	4
Endometrial polyp	8 (6.8%)	0 (0%)	6 (7.8%)	3 (7.9%)	17
Hyperplasia simplex	9 (7.7%)	3 (60%)	6 (7.8%)	2 (5.3%)	20
Hyperplasia complex with atypia	2 (1.7%)	0 (0%)	0 (0%)	0 (0%)	2
Hyperplasia simplex+complex	11 (9.4%)	3 (60%)	6 (7.8%)	2 (5.3%)	22
Endometrial carcinoma	2 (1.7%)	0 (0%)	0 (0%)	0 (0%)	2
Hyperpl. simplex+ complex+endom. cc.	13 (11.1%)	3 (60%)	6 (7.8%)	2 (5.3%)	24
Total	117	5	77	38	237

Table 6. **Histological diagnosis of postmenopausal patients with bleeding disorders - results of fractionated curettage (cervical mucosa)**

	Untreated (%)	*Estrogen (%)*	*Sequential combined (%)*	*Continuous combined (%)*	*Total*
Not evaluated	9 (7.7%)	1 (20%)	0 (0%)	10 (26.3%)	20
No epithelial alteration	66 (56.4%)	2 (40%)	45 (58.4%)	16 (42.1%)	129
Squamous metaplasia	11 (9.4%)	0 (0%)	7 (9.1%)	5 (13.2%)	23
Chronic cervicitis	17 (14.5%)	1 (20%)	9 (11.7%)	1 (2.6%)	28
Cervical polyp	6 (5.1%)	1 (20%)	13 (16.9%)	6 (15.8%)	26
Microglandular hyperplasia	3 (2.6%)	0 (0%)	1 (1.3%)	0 (0%)	4
Epithelial dysplasia (in situ carcinoma) in endocervix	2 (1.7%)	0 (0%)	1 (1.3%)	0 (0%)	3
Epithelial dysplasia (in situ carcinoma) in portio	3 (2.6%)	0 (0%)	1 (1.3%)	0 (0%)	4
In situ cc. endocervix+portio	5 (4.3%)	0 (0%)	2 (2.6%)	0 (0%)	7
Cervical adenocarcinoma	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0
Epidermoid carcinoma of portio	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0
Total	117	5	77	38	237

It was in 1961 that scientists proved the capacity of progesterone to counteract the proliferative effect of estrogen on the endometrium. Nevertheless, estrogens were used in monotherapy to relieve climacteric complaints until 1975. Since then combined preparations have taken ground and spread; estrogen monotherapy is now used under limited circumstances.[12,24,47]

Estrogen has a proliferative effect on the endometrium glands as well as on stroma. The proliferative activity of the endometrium is preserved after the menopause;[41] in our own sample, proliferating mucous membrane among those bleeding was found in 28.7% of the patients.

The higher incidence of proliferative and hyperplastic endometrium in the period of postmenopause can be attributed to the fact that, by menopause drawing near, estrogen levels stay close to the normal one and the anovulatory cycles become more frequent. On such occasions, the endometrium is exposed to continuous estrogen effect for a longer time, which may result in hyperplasia and even adenocarcinoma. In our sample, among the postmenopausal women less simplex and complex hyperplasia cases were detected in the sequential combined treatment group than in the non-treated one and even less in the continuous combined treatment group, although the differences were statistically not significant. This finding supports the presumption that hormone replacement therapy started in due time, sometimes even before the menopause, can decrease the chances for the development of hyperplasia. It is possible that progesterone, administered to counteract the effect of estrogen, can also counteract endogenous estrogen and thus decrease the risk of endometrial carcinoma below the original level. A higher level of endogenous estrogens can be expected in conditions such as estrogen-producing tumors, early menarche, late menopause, polycystic ovarian syndrome (PCOS), nulliparity due to anovulation and, particularly, obesity.[12.] It should be noted, however, that the progression of hyperplasia simplex into endometrial carcinoma is very rare, it may take years to develop and even women with regular periods can have a hyperplastic endometrium.[12]

Natural estrogens to be applied in postmenopausal hormone replacement therapy are at our disposal in various forms. These preparations contain 17-beta-estradiol. Among women who take estrogen alone, the proportion of endometrial hyperplasia is seen at 10% after 12 months of drug use, and it increases up to 50% after 24 months. Although our sample is too small for a statistical analysis, it should be mentioned that of the 5 patients using estrogen exclusively, 3 were found to have developed hyperplasia leading to irregular bleeding. According to the longest study, hyperplasia was detected in 62% of women after 3 years, more than half of them being complex or atypical.[49] An already existing hyperplasia is exacerbated, its progression is accelerated by unopposed estrogen treatment, so complex hyperplasia in association with atypia may emerge after the 4th month of treatment.[6]. In a few years, unless treatment is discontinued, the condition may progress to a stage when endometrial carcinoma is diagnosed. On the other hand, the discontinuation of treatment results in the regression of hyperplasia, but an increased risk of tumor formation persists for years since atypia does not disappear completely. According to certain observations, in women who do not exhibit endometrial changes at the start of estrogen monotherapy, the newly discovered cases of endometrial carcinoma stand at 10 in 1000 postmenopausal women after 10 years of treatment, while the relevant figure in non-treated patients is 1/1000.[40] Therefore, unopposed estrogen treatment causes the hyperstimu-

lation of the endometrium, which makes the long-term prognosis bleak. Unopposed estrogen treatment should not last longer than 3 months, because after that period of time hyperplasia cannot be kept under control; in such cases endometrial hyperplasia in association with atypia develops in 4 months the earliest.[6,42]

In postmenopausal hormone treatment, progestogens are given to prevent endometrial hyperplasia caused by estrogen. In women having undergone hysterectomy, thus lacking a functioning endometrium, progestogen supplementation, however, has undesired consequences since it interferes with the beneficial effects of estrogens on lipoprotein composition, atherosclerosis and vascular tone. Progesterone reduces the number of estrogen receptors by inhibiting their synthesis in the endometrium previously exposed to the effect of estrogens.

Progestogen preparations contain one of the following substances: progesterone-C21 steroids (micronized progesterone, dydrogesterone, medroxyprogesterone acetate) or nortestosterone-C19 steroids (norethisterone, levonorgestrel). They all exhibit a dose-dependent endometrium-protective effect.

The histological picture of the endometrium may range on a wide scale between proliferation and secretion if progestogen and estrogen are simultaneously present. To maintain hormonal balance, an increased dose of estrogen can be followed by an increased dose of progestogen.[46]

According to current views, progesterone treatment should include minimum 12-14 days a month; at least that much time is required to stop the cell cycle of the glands.[17] It is advisable to give progestogen from the start of treatment to prevent negative changes of the endometrium.

If continuous estrogen doses are supplemented by progesterone in the second half of the cycle (sequential combined treatment), withdrawal bleeding can be expected in each patient. In ideal cases, it is a regular and predictable event, therefore it does not make cooperating with the patients difficult. During sequential combined therapy, withdrawal bleeding starts after a 12-14-day course and the subsequent discontinuation of progesterone, a hormone manufactured by the corpus luteum, which is responsible for sloughing off the upper portion of the lining of the uterus. As it was mentioned, bleeding occurs after discontinuing progestogen, it lasts for 6-8 days and does not present at any other time beyond this period.

The duration and intensity of intermediate bleeding during treatment are influenced by the applied hormones, while the appearance of withdrawal bleeding depends solely on the withdrawal of a single component, progestogen in the preparation.[44] The type and administration of progestogen also play a role: compared to the patients taking medroxyprogesterone acetate, bleeding lasts shorter in women receiving dydrogesterone. As far as the risk of endometrium carcinoma is considered, cyclic combination of 2 mg of oral 17-beta-estradiol and 10 mg of dydrogesterone does not cause endometrium hyperplasia.[14] In contrast, 10 mg of medroxyprogesterone acetate or 200 mg micronized progesterone administered for 12 days per month were found safe for 3 years while 5 mg of medroxyprogesterone acetate proved its effect for only a year.[47]

During postmenopausal sequential hormone treatment, time-dependent appearance of endometrial hyperplasia can be expected, which poses an increased risk for the development of endometrial carcinoma since the prevention of osteoporosis requires 10 years of treatment. Therefore, sequential treatment is indicated in the frame of short-term palliative therapy to relieve complaints in the climacteric.[11]

Since it is not physiologically necessary to have regular periods any longer, and also because cooperation with the patients may be disturbed if the methods one applies are accompanied by bleeding, postmenopausal treatment has recently been aimed at decreasing or even stopping bleeding. To achieve amenorrhea, the tissue cycle of the endometrium, involving the growth of glands as well as proliferation of the stroma, has to be stopped at a very early stage. Therefore, progestogen has to be administered with estrogen on a daily basis (continuous combined therapy), in a large enough dose to achieve the inhibition of glandular cell division but, at the same time, it should be small enough to prevent the secretional transformation of the endometrium. This way it is possible to "produce" an underdeveloped endometrium which remains inactive due to mitotic activity and amenorrhea lasting for years can be achieved. This method of treatment is often complicated with unpredictable spotting or breakthrough bleeding (50-80% of the cases), especially in the first twelve months of therapy, which often leads to discontinuing the treatment.[48] A few women may have spotting after the first twelve months, but it is often due to missing some tablets or taking them differently from what the doctor recommended in order to reduce bleeding.

As early experience suggests, neither short-time (3-5 years) nor long-time continuous combined estrogen-progestogen treatment increases the risk of developing endometrial carcinoma, although there have been fewer studies devoted to long-term effects.[35] In a three-year study it was found that the administration of 0.625 mg CEE and 2.5 mg medroxyprogesterone had not led to the development of hyperplasia in treated women in the three-year follow-up period, and this was achieved by progestogen doses of 2.5 mg.[49] If the primary aim was to decrease the intensity of bleeding, 5 mg doses were applied.[23] If the oral administration of 100 mg micronized progesterone and percutaneous application of 1.5 mg 17-beta-estradiol was chosen, hyperplasia was absent, similarly to the combined administration of 2 mg of 17-beta-estradiol and 1 mg norethisterone acetate. Treatment using 1 mg 17-beta-estradiol and 0.5 mg norethisterone acetate could significantly decrease the fre-

quency of irregular periods; 80% of the women did not have periods after 9 months of treatment.[23]

In theory one should not expect bleeding during continuous combined treatment as the permanent administration of hormones results in an atrophic endometrium. Since female reproductive hormones are in an intricate balance with one another, just a little disturbance of this balance may cause "breakthrough" bleeding. In this case, the disorder manifests itself in the form of spotting or an amount of blood larger than just spotting. In our sample, the incidence of endometrial atrophy (presuming that endometrial atrophy can cause either endometrial atrophy or not evaluable histological findings) was significantly higher among women treated with continuous combined preparations; atypical epithelial changes were not found in any of the treated patients, which can be regarded as an advantage of combined preparations. However, the higher incidence of bleeding mentioned in the literature, a disadvantage of such preparations, could not be justified in our sample. In the fertile period, menstruation involves the upper two thirds of the endometrium and is characterized by necrotic tissue and thrombi, an effect of proteolytic enzymes released by inflammatory cells.[13] In contrast, bleeding appearing during postmenopausal hormone treatment involves only the uppermost regions of the endometrium. In breakthrough bleeding the sloughing off of the endometrium is thought to be focal, while diffuse sloughing off causes intermediate bleeding.[20]

Studying the fragility of endometrial vessels it was found that in women complaining of menstrual irregularity the density of endothelial cells in the endometrium was significantly lower millimeter by millimeter, and only one third of such cells were organized into blood vessels. Decreased smooth muscle actin-alpha was detected in the cells forming the vessel walls, which also led to an increased fragility of the vessels.[22] As natural estrogens and synthetic gestagens are equally used in hormone treatment, a disturbed balance of substances responsible for the maturation of endothelial cells results in the malformation of the vessels, which causes bleeding.[28] Changes in the extracellular matrix are also seen.[8,21,51]

Irregular bleeding in women receiving hormone replacement therapy is due to the irregular application of such hormones in a lot of cases; in some other instances, uterine tumor may lie in the background of bleeding, therefore the cause must always be revealed.

There are several organic reasons that can cause irregular bleeding (endometritis, microerosions, polyps, leiomyoma, atrophy and carcinoma). Functional changes such as the dominance of estrogen or progesterone may also be a cause. According to the literature, it is polyps and myoma (organic changes of the endometrium) that most often cause bleeding. These changes were reported as being more frequent among women not receiving hormone replacement therapy.[34] The presence of endometrial polyps is explained by the continuous estrogen stimulation of the endometrium; the majority of endometrial polyps in women in the menopause are benign.[1,36] In a large study on 1415 women aged between 23 and 85 years, who had undergone fractioned abrasion for irregular bleeding, endometrial polyps were found in 8.9% of the cases.[1] In our own sample the incidence of endometrial polyps was 6.8%, 7.8% and 7.9% among patients in the non-treated group, taking sequential combined and continuous combined preparations, respectively. Cervical polyps were more commonly found among the sequential combined and continuous combined treatment groups compared to non-treated patients.

The frequency of irregular bleedings is in correlation with the duration of the menopause. The incidence of irregular bleeding is highest after six months of the last period and a gradual decrease is noted afterwards; three years later it reaches a low rate (2). On the other hand, there is no significant difference in the incidence of irregular bleeding among patients receiving continuous combined therapy as far as the length of time since the onset of the menopause is concerned.[23]

Endometrial carcinoma is the most commonly occurring tumor in women. It may develop in both women receiving and not receiving hormone replacement therapy, but its mortality rate is lower and prognosis is better among women receiving treatment, which is possibly due to the fact that the patients regularly go to check-ups, so a detailed investigation can be performed as soon as the first bleeding appears and tumorous changes can be diagnosed at an early stage.[17] If due to regular check-ups the attending physician discovers and diagnoses endometrial carcinoma before the onset of irregular bleeding, the chances of 5-year survival are significantly improved.[25]

Our results show that due to estrogen monotherapy pushed into the background, hormonal treatment is not a factor of risk for tumorigenesis; on the contrary, combined hormone replacement therapy seems to be beneficial in the prevention of endometrial carcinoma. Although statistically not significant, our data show a trend that women given continuous combined hormone replacement therapy have a lower rate of hyperplasia and, consequently, a lower chance to develop carcinoma compared to postmenopausal non-treated women.

In the histological findings of cervical mucosa abrasion future investigation on a bigger sample is considered in the future.

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