The investigation of healthy and pathological human endometrium in the postmenopause

PhD Thesis

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Introduction

Over the past centuries life expectancy of women has increased significantly, however, the onset of menopause has not changed (in Hungary at around 50-52 years of age). One third of women's life is lived without ovarian estrogen exposure. The frequency of pathologies, characteristic for menopause is increased. In the gynecologic practice postmenopausal bleeding is of significance. According to literature data endometrial atrophy is considered to be the main cause of postmenopausal bleeding. Organic pathologies, such as endometrial polyps, uterine fibroids, and occasionally endometrial hyperplasia may also contribute to abnormal postmenopausal uterine bleeding. In about of 10 per cent of cases the underlying endometrial cancer may present with abnormal uterine bleeding.
Follow-up of patients, treated with menopausal hormone therapy is also an important gynecologic issue over the perimenopausal ages.
For good compliance endometrial safety (amenorrhoea during treatment) is utmost during postmenopausal hormonal therapy . Unopposed estrogen exposure to the endometrium results in endometrial hyperplasia and carcinoma. For this reason continuous combined treatment (fixed daily dose of estrogen plus progestogen supplemetation) is indicated for non-hysterectomized women. In addition to the classical schemes of HRT over the past decade new drugs were implemented into postmenopausal hormonal clinical practice, including tibolone and SERMs. In response to postmenopausal HRT endometrial atrophy develops. Despite this effect in a significant proportion of patients abnormal uterine bleeding occurs and patients cease HRT. Exact causes of abnormal uterine bleeding during continuous combined treatment are mostly unknown. Structural abnormality is usually not associated.

Aims

The objective of my thesis was to investigate the interaction between sonographic endometrial morphologic changes and cellular hormonal mechanisms and the impact of postmenopausal HRT on these. The following aims were addressed:

1. Is there any difference between healthy postmenopausal women and patients with postmenopausal uterine bleeding in circulating serum hormone levels (FSH, E2, progesterone)?
2. Is there any correlation between endometrial thickness measured by transvaginal ultrasound (TV-US) and histopathologic findings in patients treated for postmenopausal beeding ?
3. Is 3D ultrasound measurement of endometrial volume feasible for early detection of endometrial pathologies ?
4. What are the molecular mechanisms of endogenous estrogen action within human endometrium during postmenopause ?
5. What is the action of non-genomic ERalpha/PI3K/Akt signaling pathway in healthy and pathologic human endometrium and in response to continuous combined HRT and tibolone therapy ?

6. Finally, to test, whether investigation of genomic and non-genomic effects of estrogens in the postmenopausal endometrium may predict a future abnormal uterine bleeding as a result of benign proliferative endometrial changes and of endometrial cancer.

Patients and methods

Patients

At the Department of Obstetrics and Gynecology of the University Medical School of Pécs between March, 2005 and January 2007 one-hundred and twenty four postmenopausal women were enrolled in the study.

Group I. consisted of 50 patients with postmenopausal uterine bleeding.

Group II. consisted of 38 postmenopausal women without uterine bleeding to serve as controls.

Group III. was the postmenopausal HRT group of 36 patients, of whom 27 patients were treated with continuous combined treatment (1 or 2 mg of crystallized 17beta-estradiol/1mg norethisteron-acetate) and 9 patients with tibolone in a dose of 2.5 mg/day, respectively.

Serum hormone measurement

FSH, estradiol (E2) and progesterone levels in serum of patients were determined by radio-immunoassay (Byk-Sangtec Diagnostica, Dietzenbach, Germany).

TV 2D US examination

TV US was performed prior to histologic endometrial sampling by Kretz Voluson 730 real-time ultrasound scanner (Kretz Technik AG., Zipf, Austria) in lithotomy position of patients with an emptied urinary bladder. Endometrial thickness was measured with a 5-8 MHz endovaginal transducer in midsagittal view of the uterus using ’double-layer’ technique.

3D volumetry

The 3D volume measurement of the endometrium was done using VOCAL software of the 3D ultrasound scanner after visualizing the endometrium in midsagittal view with a 5-8 MHz endovaginal volume transducer (90° field of view). The 3D mode was activated and the mobile sector was set to cover the region of interest (ROI), the volume sector angle was set as 60° and the fast volume acquisition was used to avoid motion-artifacts. After volume acquisition 3D volumes were immediately stored in RAM memory of the equipment. Volume measurements were done off-line from reloaded volumes with the simultaneous analysis of the three ortogonal planes. With the VOCAL software the A-plane was selected to be the reference image, the two poles were determined with the caliper to fix the axis of rotation, then the manual contour mode was engaged, and 6 rotational steps (per 30°) were selected to draw the contour lines of the rotated planes. After editing the 6 contours the virtual 3D image was visualized by the software with the respective ROI-volumes.

Endometrial sampling

Endometrial samples were retrieved by the following methods, approved by the Institutional Review Board on Human Research of the University of Pécs:

1. In patients with abnormal uterine bleeding endometrial samples were collected during diagnostic curettage or hysterectomy (if endometrial cancer was ruled out by histology within 6 months).
2. Patients with benign gynecologic leasions (uterine prolapse, fibroid, ovarian cysts) undergone hysterectomy served as controls together with healthy patients, seen at our menopausal outpatient clinic as potential candidates for HRT. Endometrial samples were retrieved after written informed consent had been obtained following routine gynecologic cervical cancer screening.
3. Endometrium biopsy was done at yearly check-up of patients receiving menopausal hormone therapy.

Endometrium biopsy was accomplished using „Suresample" Wallace Endometrium Sampler Set. Histopatholgic examinations were perfomed et Department of Pathology of the University Medical School of Pécs.

The receptor studies

The individual tissue samples were homogenized at 4°C in 1ml/100 mg tissue of ice cold Buffer I (50 mM Tris-Cl pH 8.0, 1mM Na-orthovanadate) for 30-40 sec, then we added 1ml/100 mg tissue of ice cold Buffer II (10mM Tris-Cl pH 8.0, 1mM EDTA, 1%SDS, 5% mercaptoethanol, 40% glycerol) was added and the samples were homogenized further bathed in boiling water for 5 min and centrifuged. Supernatants were stored at -20˚C. After electrophoresis and blotting the membranes with the transferred proteins were treated with primary antibodies. As secondary antibody we used anti-rabbit antibody conjugated with IgG conjugated HRP. Blots were developed and visualized by chemiluminescence (ECL). Western blot analyses were conducted at least three times in three independent preparations of tissues with comparable results.

Statistics

The data are presented as mean ± S.D. Group differences were analyzed by ANOVA followed by Student-Newman-Keul's multiple range tests. Pearson's correlation test was used to analyze the relationship between the obtained changes. Differences were considered to be statistically significant at $P<0.05$ levels.

Results

1. Clinical data

We found significant difference between group I. (postmenopausal uterine bleeding) and group II. (control postmenopausal women) in mean age, time and length of menopause, body weight, and in body mass index.

There was no significant difference between group II. (controls) and group III. (HRT-patients) in clinical characteristics.

Clinical characteristics of patients

	Group I. n=50	Group II. n= 38	Group III. n=36
Mean age (years)	63.8±7.6	56.3±5.5	56.6±5.8
Bodyweight (kg)	84.8±12.6	72.6±9.8	70.9±8.8
Body Mass Index (kg/m2)	31.3±4.3	25.1±5.2	27.0±4.8
Number of gravidities (n)	4.2±1.8	4.1±2.1	3.3±1.9
Number of deliveries (n)	2.1±1.9	2.1±1.8	1.9±1.8
Menarche (years)	14.6±1.8	14.8±1.9	14.6±1.9
Onset of menopause (years)	53.1±3.1	50.2±2.5	49.7±3.9
Length of menopause (years)	13.3±6.8	4.8±3.7	4.9±4.9
Duration of HRT (years)	-	-	4.2±2.1

2. Results of serum hormone levels

In group I. FSH levels were significantly lower and estradiol levels were higher, respectively, compared to that of group II. Progesterone levels were higher in group I., but the difference did not reach statistical significance.

Levels of serum hormones

Serum hormone	Group I. n=50	Group II. n= 38	Group III. n=36
FSH (U/l)	58.40±25.38	78.17±44.50	58.9±39.91
Estradiol (pmol/l)	69.52±51.61	40.47±49.37	128.02±136.24
Progesterone (nmol/l)	0.92±0.84	0.59±0.48	0,79±0.49

3. Comparison of sonographic and histologic endometrial findings
Uterine size and mean endometrial thickness were significantly greater in group I. compared with groups II. and III.

Results of uterine size, endometrial thickness, and histologic finding

	Group I. n=50	Group II. n= 38	Group III. n=36
Mean uterine size (cm)	7.66±3.4	6.81±2.1	6.75±2.0
Mean (range) endometrial thickness (mm)	10.4(3.2-26)	4.1(1-16.5)	3.9 (1-7.3)
Histopathologic finding			
Normal endometrium (n)			
Proliferative endometrium	4	2	
Blood discrasia in endometrium	5		
Inactive secretory endometrium		3	3
Irregular secretory phase	2	4	10
Regressive endometrium		8	8
Endometrial atrophy	3	9	15
Cystic endometrial atrophy	4	8	
Endometrial polyp	5	2	
Endometrial hyperplasia			
Simplex	9	2	
Glandular-cystic	3		
Atypic	2		
Endometrial carcinoma	13		
∑	50	38	36

Distribution of endometrial thickness and histopathologic finding

Endometrial thickness	Normal endometrium (n)	Benign change (n)	Atypia (n)	Malignancy (n)
≤4mm	72	1		
4,1-8mm	10	13		
8,1-12mm		9	2	1
12,1-16mm		2		1
16,1-20mm				5
≥20mm				6
∑	82	25	2	13

4. With respects to endometrial hyperplasia and carcinoma significant correlation was found between endogenous estradiol levels and histopathologic findings.

The serum hormone levels and endometrial pathology

Serum hormone	Normal endometrium (n=52)	Endometrial polyp (n=7)	Endometrial hyperplasia (n=16)	Endometrial carcinoma (n=13)
FSH	67.22±37.36	66.13±8.95	67.75±44.03	59.79±28.97
Estradiol	57.03±54.05	52.81±4.14	97.87±74.02	62.71±56.13
Progesterone	0.76±0.72	0.96±0.75	0.85±0.35	0.83±0.88

5. Results of three-dimensional ultrasound volumetry

In group I. significantly larger endometrial volumes were measured by 3D-sonography compared to that of group II. and III. There was no significant difference in endometrial volume between groups II. and III. In group III. endometrial volume was slightly greater among patients treated with continuous combined hormone treatment compared with tibolone-treated patients.

Endometrial volume in the study groups

	Group I. n=50	Group II. n= 38	Group III. n=36	
			CCHT n=27	tibolon n=9
Mean endometrial volume (ccm)	10.6±16.5 (5.6-66.2)	2.6±3.4 (1.7-10.1)	2.4±1.5 (1.3-3.2)	2.3±1.4 (0.9-2.5)

CCT: Continuous combined hormone treatment

Mean endometrial volume was significantly greater in patients with endometrial pathologies compared to those, who had a negative histologic finding. Based on our results the cut-off value of volume for endometrial carcinoma was found to be 12.1 ccm, below this volume no endometrial malignancy was detected.

Endometrial volume and different endometrial pathology

Histopathologic finding	Mean (range) endometrial volumen (ccm)
Normal endometrium (n=82)	1.9(0.9-2.4)
Endometrial polyp (n=7)	6.8(7.8-9.6)
Endometrial hyperplasia (n=20)	8.5(5.8-14.1)
Endometrial carcinoma (n=13)	19.4(12.1-66.2)

6. Results of the receptor studies

The expression of pAkt was significantly higher in the proliferative phase of the menstrual cycle compared to that of the secretory phase and postmenopause. Similar significancy was not detected with respect to pER. Our results suggested, that there was significant correlation between changes of pAkt and serum estradiol levels. We found parallel changes between the expression of pAkt and pERalpha.

The expression of pAkt and pERalpha was significantly higher in group III. (HRT patients) compared with group II. (controls). There was no difference in ERalpha levels between HRT-treated and control patients.

With the analysis of endometrial histologic findings and expression of pERalpha and pAkt we found, that in proliferative endometrial changes the activation was abundant compared to that

of contol patients with atrophic endometrium, however, there was no statistically significant correlation, if benign and malignant histopathologic findings were compared.

Conclusions

1. In patients with postmenopausal uterine bleeding serum estradiol levels are significantly higher compared to that of healthy postmenopausal women. This finding substanciates the fact, that changes of endogenous estrogen levels (that might be influenced by many factors) have significant impact on proliferative changes of the postmenopausal endometrium. Continuous unopposed estrogen exposure to the endometrium results in endometrial hyperplasia, moreover, endometrial carcinoma may develop. For the early detection of endometrial cancer it is crucial to screen high-risk patients: obese, endometrial hyperplasia in the case history, HRT and tamoxifen treatment.
2. Endometrial thickness as measured by transvaginal sonography is considered to be a biomarker with respect to estrogen exposure, and its measurement is applicable for the examination of proliferative activity of the endometrium. Endometrial thickness showed good correlation with pathologic endometrial histologic findings. Below 4mm cut-off value of endometrial thickness only one case of endometrial hyperplasia was diagnosed. No case of endometrial carcinoma was detected below 8 mm of endometrial thickness. Transvaginal ultrasound examination is of value to pick up high-risk patients for endometrial pathologies, even in patients without sign and symptoms. Further examination of suspect cases with histology (curettage) or with endometrial sampling by biopsy will help us to conclude to the final diagnosis.
3. Three-dimensional ultrasound volumetry is helpful in the early detection of postmenopausal endometrial pathology, and allows more exact calculation compared to 2D-scan. Although expensive and time-consuming 3D-volumetry is not recommended for routine screening, but it is a definitely helpful adjunct to the differencial diagnosis of abnormal uterine bleeding.
4. The results of our receptor studies strongly suggest, that non-genomic effect of estradiol is active even in the human postmenopausal endometrium.
5. The activity of Akt/PKB and of estrogen receptors shows parallel changes with serum estrogen levels.
6. Based on our findings phosphorylation of Akt and ER (activity) is increased in response to HRT (continuous combined estrogen+progesterone treatment) in spite of relatively low estradiol levels. Endometrial sampling via biopsy as part of routine gynecologic screening and further molecular biologic examination of non-genomic effects of estrogen may be feasible to predict the prognosis of an early-stage endometrial proliferative disease.

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