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HORMONE REPLACEMENT THERAPY WITH CLIMEN© AND ITS EFFECTS ON THE BREAST TISSUE

HORMONSKO NADOMJESNO LIJEČENJE CLIMENOM© I NJEGOV UČINAK NA TKIVO DOJKE

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Professional paper

Key words: hormone replacement therapy, estrogens, progestogens, breast tissue, mammography, ultrasound

Summary. ***Objective.*** To evaluate the effect of the hormone replacement therapy on breast changes in postmenopausal women. ***Material and methods.*** The study includes 35 women with natural or surgical menopause who were treated with sequential estrogen/progestogen hormone replacement therapy (E/P HRT) during one year. The therapeutic program consisted of three weeks treatment with estradiol valerate 2 mg/day orally, combined with ciproterone acetate 1 mg/day in the last 10 days (Climen© – Schering) followed by one week pause. Before the start with E/P HRT basic mammography and ultrasound examination of the breast tissue was performed in all patients. At the end of the study after 12 therapeutic cycles, control mammography and ultrasonographic examination were done. ***Results.*** In the short-term study 18 patients (51.43%) showed regression of the finding, 15 (42.86%) stagnation, and only 2 (5.71%) progression of the finding (D=0.27, p<0.01). ***Conclusion.*** A clear consensus regarding the relationship between HRT and breast cancer risk cannot yet be drawn.

Stručni članak

Ključne riječi: hormonsko nadomjesno liječenje, estrogeni, progestogeni, dojka, mamografija, ultrazvuk

Sažetak. ***Cilj rada*** je bio vrednovati učinak hormonskog nadomjesnog liječenja na promjene dojke u 35 žena u postmenopauzi. ***Bolesnice i način istraživanja.*** 35 žena u prirodnoj ili kirurškoj postmenopauzi je kroz jednu godinu liječeno sekvencijskom hormonskom nadomjesnom terapijom (HNL). Terapijska shema je bila tri tjedna estradiol valerijanat 2 mg/dan peroralno, kombinirano s ciproteron acetatom 1 mg/dan posljednjih 10 dana (Climen© – Schering) te nakon toga sedam dana stanke. Prije početka HNL svima je pacijenticama učinjena mamografija i ultrazvučni pregled dojki. Na kraju studije, nakon 12 terapijskih ciklusa, učinjeni su kontrolna mamografija i pregled ultrazvukom. ***Rezultati.*** U kratkoročnoj studiji u 18 pacijentica (51,43%) nastupila je regresija nalaza, u 15 (42,86%) stagnacija i u 2 (5,71%) pacijentice progresija nalaza (D=0,27, p<0,01). ***Zaključak.*** Jasni dogovor u pogledu odnosa između hormonskog nadomjesnog liječenja i raka dojke još se ne može donijeti.

Introduction

Breast cancer is one of the most frequent cancers in the female population. Approximately one of every 10–12 women will develop this type of cancer during her life, its incidence is highest in the premenopausal period. More than 25 % of all cases of breast cancer occurred before 50 years of age.[1] Although there are more different theories explaining the connection between the female sexual hormones and the risk of breast cancer, the specific role of the estrogens and progestogens in this process have never been cleared enough. Estrogens stimulate the breast tissue through their own estrogen receptors and the effect of this stimulation is a proliferation of the ductal and alveolar epithelium. Estrogen receptor-transmission mechanisms are shown as regulators of the effects of many different substances, such as: transforming growth factor alfa, transforming growth factor beta, enzymes (cathepsin D, and plasminogen activator), prooncogenes (c-fos, C-mis i HER-2/neu). As a result, the value of mRNK increases several hours after the estrogen administration.[1] Progesterone in the second part of the menstrual cycle induces dilatation of the ductal system and secretory transformation of the alveolar cells; in the menstrual phase there is some exfoliation of the alveolar cells, similar to those of the endometrium. Progestogens regulate estrogen receptors on a very low level, so they interfere with estrogen receptor transmission activity on proto-oncogenes. The ratio of the two progesterone receptor isoforms, PRA/PRB may define the response to progesterone in breast tissue. Isaksson and al.[2] measured the immunohistochemical expression of PRA and PBA in postmenopausal cynomolgus macacas, treated for 35 months with conjugated equine estrogens (CEE), tamoxifen or medroxyprogesterone acetate (MPA, CEE + MPA) and found: unchanged levels of PRA in CEE and a decline in the CEE/MPA group. The mean PRA/PRB in the CEE group was 2,7, and in CEE/MPA group 0,2.

Syndrome of fibrocystic breast (Reclus-Cooper's disease) is a benign disease. The first stage of development

of the disease is mastodynia with cyclic premenstrual symptoms and histological feature of oedema and proliferation of the perilobular fibrose tissue. If progesterone is given, symptoms disappear or are reducing. The second stage is a stage of pseudotumor, when the pain is not so intense, but a rough nodular stucture, benign or atypical hyperplasia of the ductal and lobular epithelium and fibrous stromal proliferation are present. The third stage is a presence of cysts, who are the result of ductal system obstruction due to fibrous stromal or intraductal proliferation. Microcystic disease is present when cysts are smaller than 20 mm in diameter, and macrocystic mastopathy when they are larger. Investigating the relationship between HRT and frequency of breast atypical hyperplasia, Gayet and al.[3] found the incidence rate significantly increased over time and significantly higher for HRT users (Odds Ratio 2.05), partly by the incidental discovery of these lesions by mammography and partly by a real increase of the disease.

Regarding the possible connection between hormone replacement therapy (HRT) and breast cancer, the analyses show that the relative risk is approximately 1,08 to 1,30, but there are almost the same number of studies showing insignificant reduction of the risk of breast cancer during HRT.[4] Most authors agree that women who have taken HRT less than 5 years, don't have any risk of breast malignomas. On the other hand, there are different attitudes if the HRT is taken more than 5 years. The Women's Health Initiative trial[5] of combined estrogen plus progestin therapy (conjugated equine estrogens 0,625 mg/day and MPA 2,5 mg/day) found increased total hazard ratio 1,24 of invasive breast cancer compared with placebo. Seeger and al.,[6] investigating in vitro the influence of the three most used progestogens: MCA, norethisterone acetate (NET) and progesterone (P) on the human breast cancer cell line MCF-7 found that all these progestogens, given alone, displayed a significant inhibition of cell proliferation, and in combination with estradiol this inhibitory effect is lower, but still significant. It is not yet clear whether there is a difference in risk with sequentially combined versus continuously combined HRT. Seeger and al,[7] investigating the influence of progesterone and various synthetic C-19 and C-21 progestins on cell proliferation of a human breast cancer cell line in vitro, found that sequentially combined with estradiol, only chlormadinone acetate showed significant inhibitory effect on cell proliferation. Continuously combined, all progestins exhibited this inhibitory effect.

At the beginning of the 21st century, mammography screening is still the most important diagnostic method in the early recognition of breast cancer. Its advantage is in its ability to detect calcifications in the inpalpable forms of carcinomas and providing a precise information about disposition of the mammary structures, especially in the involutive postmenopausal breasts. X-rays passing through the breast tissue are being absorbed from the fibro-glandular elements, and we see a 'shadow' on mammography, whose density depends of the percentual portion of these elements. Greater quantity of connective and glandular tissue give higher density of the shadow. In opposite, fat tissue is much more permeable for X-rays and it is projected like transparent zone on mammography. According to the Wolf's classification the mammographic pictures can be classified as: N1 – predominatly fat tissue without galactofores; P1 – ductal picture is present in less than the fourth of the breast tissue; P2 – nodular and ductal parenchima in more than the fourth of the breast tisssue; DY – diffusely increased density of the breast tissue (fibrocystic disease). The aging process which is most distinctive in the postmenopausal period leads to atrophy of ductal and glandular structures which are replaced with fat tissue. HRT can change this process of aging in the breasts and can also increase the density of the breast tissue.

Material and methods

The study was designed according to the CONSORT statement.[8]

1. *Eligibility criteria for participants:* 1. At least one-year long postmenopausal period, e.g. period between last menstrual cycle and date of admitting at the Outpatient Department for Menopause in patients with natural menoapause; or previous hysterectomy with bilateral oophorectomy in a period of one month to five years before admission at our Department in patients with surgical menopause; 2. Patient's age less than 55 years; 3. Absence of some contraindication for hormone replacement therapy, as follows: otosclerosis, cholelithiasis, presence of serious liver or kidney damage, familiar history of breast cancer, personal history of breast, endometrial or ovarian cancer, the actual trombophlebitis or phlebothrombosis.

2. *The setting, location and timing where and when the date were collected:* the Outpatient Department for menopause of the Clinic of Gynecology and Obstetrics, Medical Faculty, Skopje in the period from the 1st of January 2002 to the 1st of April 2003.

3. *Precise details of the interventions for the group, how and when they were actually administered:* All patients were treated with oral sequential estrogen/progestogen hormone replacement therapy (OSeq E/P HRT) during one year. The therapeutic scheme consisted of three weeks treatment with estradiol valerate 2 mg/day orally, combined with ciproterone acetate 1mg/day in the last 10 days (Climen® – Schering) followed by one-week pause. This drug has been approved by the Republic Drug committee (RDC) of the Republic of Macedonia.

4. *specific objectives and hypotheses:* The purpose of the study was an assessment of the safety of the 28-day regimen with Seq E/P HRT with Climen® during one year regarding breast tissue. The hypothesis was: this HRT regimen has not any serious adverse effects on the breast.

5. *Clearly defined primary and secondary outcome measures, any methods used to enhance the quality of measurements:*

Before the therapy, the evaluation of all women included:

Table 1. Demographic data: age, duration of the postmenopause, parity, smoking habits and alcohol, body mass index, systolic/diastolic blood pressure, type of menopause (natural, surgical) in 35 postmenopausal patients
Tablica 1. Demografski podaci: dob, trajanje postmenopauze, paritet, navike pušenja i pijenja alkohola, indeks tjelesne težine, sistolički/dijastolički krvni tlak, vrsta menopauze (prirodna, kirurška)

Age (years) Dob (godine)	47.52±3.7
Duration of the postmenopause (months) Trajanje postmenopauze (mjeseci)	29±6.20
Parity – Paritet	2 (0 to 5)
Smokers – Pušačice	10/35
Alcohol consumers Potrošačice alkohola	2/35
Body mass index (BMI) Indeks tjelesne težine	27.81±3.84
Systolic / Diastolic blood pressure (mmHg) Sistolički/Dijastolički krvni tlak	92.23±11.20 / 146.11±24.60
Natural / Surgical menopause Prirodne / Kirurške menopause	9/35 / 26/35

1. *A standardized structured protocol questionnaire* for menopause designed according to the recommendations by the Europian Society for Menopause, which include:

   Demographic data (Table 1.): age, duration of the postmenopausal age, parity, smoking habits and alcohol consuming, sport, diet, body mass index, systolic/diastolic blood pressure, type of menopause (natural, surgical). In each patient the body mass index was determined:

$$\text{BMI} = \frac{\text{body weight (g)}}{\text{body height (cm)}^2}$$

   Kupperman index for the menopausal symptoms assessment, represented on the *Table 2.*

   Familiar history for coronary disease, osteoporosis, breast cancer, colorectal cancer or endometrial cancer, Alzheimer sclerosis, cerebrovascular insult *(table 3.)*.

   Personal history for previous or present diseases, such as: coronary disease, hepatic or kidney disease, therapy with corticosteroids, thyroid gland disease, postgastrectomy malabsorption syndrom, Cushing's disease, thromboembolism or phlebothrombosis, osteoporotic fracture, breast cancer, genital cancer, colorectal cancer, otosclerosis, cholelithiasis, genital prolapse, urine incontinence, hyperparathyroidism and history for present sexual life: dyspareunia, decrease of the libido, absent orgasm *(Table 4.)*.

2. *Complete evaluation for possible contraindications for HRT:* 1. Abdominal ultrasound for excluding: cholelythiasis, hepatic damage (cirrhosis, hepatic metastases), abdominal tumors; 2. Complete laboratory analyses for hepatic and kidney function, such as: alkaline phosphatase, acid phosphatase, ALT, AST, LDH, serum urea, serum creatinin, serum uric acid; 3. some parameters of the coagulation status, such as:prothrombin time (PT) that is expressed into: absolute value, percentage and INR; activated partial thromboplastin time (aPTT Pathrombin SL); thrombin time and platelets number; 3. complete gynaecological evaluation, including: cervical smear and colposcopy, gynaecologic ultrasound of the pelvis for excluding uterine and ovarian tumors, and

Table 2. Kupperman's postmenopausal index
Tablica 2. Kuppermanov postmenopauzalni indeks

Factors/points	Absent Nema	Mild Blagi	Moderate Umjereni	Intensive Jaki	Unbearable Nepodnošljivi	Points Bodovi
Hot flashes – Vrući valovi	0	4	8	12	16	
Paresthesia – Trnci	0	2	4	6	8	
Insomnia – Nesanica	0	2	4	6	8	
Nervousness – Živčanost	0	2	4	6	8	
Depression – Potištenost	0	1	2	3	4	
Vertigo – Vrtoglavica	0	1	2	3	4	
Fatigue – Umor	0	1	2	3	4	
Joint pain – Zglobne boli	0	1	2	3	4	
Headache – Glavobolja	0	1	2	3	4	
Palpitation – Lupanje srca	0	1	2	3	4	
Climax mild: sum 15–20 points – blagi: zbroj 15–20 bodova moderate: sum 21–35 points – umjereni: zbroj 21–35 bodova grave: sum >35 points – teški: zbroj >35 bodova						Sum: Zbroj:

Table 3. Family history in 35 postmenopausal patients
Tablica 3. Obiteljska anamneza u 35 postmenopauzalnih bolesnica

Coronary disease – Koronarna bolest	12 – 34.3%
Osteoporosis – Osteoporoza	11 – 31.4%
Breast cancer – Rak dojke	1 – 2.9%
Colorectal cancer – Kolorektalni rak	3 – 8.6%
Endometrial cancer – Rak endometrija	1 – 2.9%
Alzheimer disease – Alzheimerova bolest	5 – 13.5%
Cerebrovascular insult – Cerebrovaskularni inzult	6 – 17.1%

Table 4. Personal history for previous or present diseases and for sexual life (n=35)
Tablica 4. Osobna anamneza za prethodne ili aktualne bolesti i za aktualni seksualni život (n=35)

Coronary disease – Koronarna bolest	3 – 8.6%
Hypertension – Hipertenzija	14 – 40.0%
Thyroid gland disease – Bolest štitnjače	2 – 5.7%
Diabetes mellitus – Šećerna bolest	6 – 17.1%
Previous thrombosis – Ranija tromboza	3 – 8.6%
Genital prolapse – Ispadanje genitala	5 – 14.3%
Stress incontinence – Stres inkontinencija	9 – 25.7%
Osteoporosis (ultrasound BDM of calcaneus decreased more than 2SD)	7 – 20.0%
Dyspareunia – Dispareunija	15 – 42.9%
Decrease of the libido – Smanjen libido	29 – 76.3%
Absent orgasm – Nepostojanje orgazma	26 – 74.3%

evaluation of the thickness of endometrium. The thickness of the endometrium more than 4 mm was indication for its histological evaluation. All the parameters were determined at the beginning, on the sixt month and at the end of the study.

3. *Breast tissue evaluation with mamography (Wolf's classification):* N1 – predominantely fat tissue without galactofores; P1 – ductal picture is present in less than fourth of the breast tissue; P2 – nodular and ductal parenchim in more than fourth of the breast tisssue; DY – diffusely increased density of the brast tissue (fibrocystic disease).

At the end of the study, after one-year Seq E/P HRT, the evaluation of all women included:

– Kupperman index for the menopausal symptoms assessment;
– Complete laboratory analyses for hepatic and kidney function;
– Same parameters of the coagulating status;
– Complete gynecologic evaluation as quoted previously;
– Breast tissue evaluation with mamography (Wolf's classification).

The determination of the definitive sample size.

Every fifth postmenopausal patient admitted at the Outpatient Department for Menopause in the period was assessed for eligibility for this HRT regiment with Climen (n=57). Seven patients were excluded from the study because they refused to participate, and eight stopped the therapy prematurely, before one year duration. So, forty two patients were randomised. Nine of them were excluded because of the presence of some contraindication for HRT: three with previous history of breast cancer, one with previous endometrial cancer, three with presence of biliar calculosis and two with great disturbance of hemostasis, like elevated plasminogen inhibitors and decreased protein C and protein S.

Every fifth postmenopausal patient was allocated into the study group according to the admission date.The sequence was discontinued when a patient was excluded because of some reasons. The authors of this study determined the allocation sequence, enrolled participants, assigned participant to this group. All participants were aware of group assignment. All subjects were given an explanation of the study and informed consent was obtained. Women who were unhappy to be randomized were excluded.

Statistic analysis was made using Student's t test and Kolmogarof-Smirnof test for one study group.

Results

Kupperman index for the menopausal symptoms during the study is represented on the *table 5*. The absence

Table 5. Sexual life (absence of orgasm) at the beginning and at the end of the study in three groups of 35 postmenopausal patients
Tablica 5. Spolni doživljaj (orgazam) na početku i kraju studije u tri skupine 35 postmenopauzalnih bolesnica

	Absent orgasm – Nepostojanje orgazma At the beginning of the study Na početku studije	At the end of the study Na kraju studije
Mild – Blagi climax	7/35 (20%)	5/35 (14.3%)
Moderate – Umjeren climax	15/35 (42.9%)	3/35 (8.6%)
Grave – Teški climax	13/35 (37.1%)	1/35 (2.9%)

Table 6. Coagulation status at the beginning and at the end of the study (n=35)
Tablica 6. Koagulacijski status na početku i na kraju studije (n=35)

Parameter Pokazatelj	Before therapy Prije terapije	After therapy Poslije terapije	t	p
Prothrombin time	10.52±2.16	10.62±2.23	0.137	NS
PT %	92.64±14.65	89.36±12.66	0.221	NS
PT INR	1.03±0.18	1.05±0.22	0.417	NS
aPTT Pathtrombin	26.66±2.23	28.19±4.47	1.789	NS
Thrombin time	13.27±1.97	15.22±1.25	14.889	<0.0001
Thrombocytes	293.33±65.18	244.22±58.15	3.283	<0.002

Table 7. Cervical Pap smear and colposcopic findings
Tablica 7. Cervikalni obrisak po Papanicolaou i kolposkopski nalaz

Pap smear – Papa Obrisak	
Atrophic smear with candida infection Atrofični razmaz s kvasničkom infekcijom	15 – 42.9%
Atrophic smear with nonsepcific infection Atrofični razmaz s nespecifičnom infekcijom	10 – 28.6%
Atrophic smear with coilocytosis Atrofični razmaz s koilocitozom	3 – 8.6%
Atrophic smear without infection Atrofični razmaz bez infekcije	16 – 45.7%
Colposcopy – Kolposkopija	
Unvisible zone of transformation Nevidljiva transformacijska zona	16 – 45.7%
Leucoplakia (biopsia: 3 parakeratosis, 2 hyperkeratosis, 1 coilocytosis)	5 – 14.3%
Normal colposcopic pattern Normalna kolposkopska slika	8 – 22.9%
Mozaic – Mozaik	1 – 2.0%
Ectopia	5 – 14.3%

Table 8. Mammographic findings and ultrasonographic examination of breast tissue in 35 users of one-year sequentional estrogen/progestagen hormone replacement therapy
Tablica 8. Mamografski i ultrazvučni nalazi 35 korisnica jednogodišnje sekvencijske estrogen/progestagenske nadomjesne terapije

Patient Pacijentica	Findings before therapy Nalaz prije terapije	Findings after therapy Nalaz nakon terapije	**Prog**ression **Reg**ression **St**agnation
1. M. D.	P1	P1	St
2. T. Z.	P1	N1	Reg
3. S. E.	DY	N1	Reg
4. J. R.	P2	DY	Prog
5. S. M.	N1	N1	St
6. K. A.	P1	P1	St
7. Z. L.	DY	DY	St
8. N. S.	P1	N1	Reg
9. S. V.	P1	N1	Reg
10. A. S.	DY	P1	Reg
11. M. Lj.	P2	P2	St
12. I. M.	P1	N1	Reg
13. S. B.	P2	P1	Reg
14. I. A.	P1	N1	Reg
15. J. N.	P1	P1	St
16. M. M.	DY	P1	Reg
17. A. M.	P2	P1	Reg
18. A. M.	P1	P1	St
19. D. V.	DY	P2	Reg
20. S. V.	P2	P1	Reg
21. S. D.	DY	DY	St
22. S. S.	P1	N1	Reg
23. D. E.	DY	P1	Reg
24. G. L.	DY	P2	Reg
25. L. Lj.	P1	P1	St
26. P. Lj.	P2	P2	St
27. H. A.	N1	P1	Prog
28. K. M.	P1	P1	St
29. D. S.	DY	DY	St
30. B. D.	P2	N1	St
31. S. S.	P2	P2	St
32. K. A.	P2	P1	Reg
33. J. R.	P2	P1	Reg
34. N. L.	P1	P1	St
35. R. A.	DY	DY	St

N1: predominantely fat tissue without galactofores
pretežno masno tkivo bez galaktofora
P1: ductal picture is present in less than fourth of the breast tissue
pojava duktusa u manje od četvrtine tkiva dojke
P2: nodular and ductal parenchima in more than fourth of the breast tissue
nodularni i duktalni parenhim u više od četvrtine tkiva dojke
DY: diffusely increased density of the breast tissue (fibrocystic disease)
difuzno povećana gustoća tkiva dojke (fibrocistična bolest)

of the orgasm was more prominent in the cases of moderate and grave climax, it has been ameliorated in most of them.

In all patients who finished the study (n=35) there were no contraindication for HRT. The laboratory examinations were in normal range at the beginning of the study, on the sixth month and at the end of the study.

The evaluated parameters of the coagulation status did not change, except the thrombin time and platelets number that significantly decreased *(Table 6.)*.

The gynecological ultrasonography of the pelvis for excluding uterine and ovarian tumors, and evaluation of the endometrial feature, performed at the beginning of the study, on the sixth month and at the end of the study was normal. The thickness of the endometrium more than 4 mm in 5 out of 35 patients at the beginning of the therapy was indication for its histological evaluation. In all four cases the hystological was »matron« polyp with atrophic endometrium.

Cervical smear and colposcopic findings at the beginning of the study are represented on the *Table 7*. A usual distribution of abnormal patterns can be seen.

On the *Table 8.* the mammographic findings and ultrasonographic examination of breast tissue in 35 users of one-year sequentional estrogen/progestagen hormone replacement therapy (Climen-Schering), before and after the therapy, are presented. As can be seen at the end of the study there were 18 cases (18/35, i.e. 51,43%) of regression, 15 cases (15/35, i.e. 42,86%) of stagnation and 2 cases (2/35, i.e. 5,71%) of progression in findings.

In the group with regression in 3 patients the dimensions of conglomerates became significantly smaller; in 5 the conglomerates disappeared completely; in 7 patients with regular findings or mastopathy at beginning of the study, there was an involutive feature at the end; in 3 patients with fibrocystic disease a significant reduction or disappearing of this condition was noticed at the end of the study.

Only two cases (2/35, v.s. 5,71%) had progressive tissue changes at the end of the study. In the first case with massive conglomerate, there was an evolution in the circumscriptive tumor with benign cytology. In the second case, a retromammilar fibrosis occurred.

Statistical analysis using Kolmogarof-Smirnof test for a study group is as follows *(Table 9.)*.

Table 9. Statistic analysis of the mamographic findings and ultrasonographic examination of breast tissue in 35 users of HRT after one-year long therapy with Climen
Tablica 9. Statistička analiza mamografskih i ultrazvučnih nalaza 35 korisnica nakon jednogodišnje sekvencijske estrogen/progestagenske nadomjesne terapije Climenom

			Relative	Relative	Cumulative	Cumulative	D p
Regression	18	11.67	18/35 = 0.51	11.67/35 = 0.33	18/35 = 0.51	11.67/35 = 0.33	0.18
Stagnation	15	11.67	15/35 = 0.43	11.67/35 = 0.33	33/35 = 0.94	23.34/35 – 0/67	0.27
Progression	2	11.67	2/35 = 0.06	11.67/35 = 0.33	35/35 = 1.00	35/35 = 1.00	0.00
Total	35	35	1.00	1.00			

For n=35 and D=0.27 the Kolmogarof-Smirnof test for one study group is with significance of $p<0.01$

Discussion

The growth of mammary tissue depends on the delicate balance between the activity of the two sex steroid hormones: estradiol and progesterone. Though the estrogens are the most potent stimulating factor for breast cell proliferation, the role of progestesterone is still the subject of professional debates. Progestins could have a positive, moderate or no effect or even an inhibitory effect on the growth of glandular tissue.

According to Lauritzen,[9] the cyclic application of progestin might have double effects: to stop the proliferation and induce a specific function of target tissue, effects which are mediated through the reduction of the estrogen receptors in breast glandular tissue, the stimulation of the transformation of the more potent estradiol into the less effective estron and through the reduction of the intracellular metabolism and blood supply. Women who recieved long-term estrogen/progestagen replacement therapy have decreased risk for development of endometrial and ovarian cancers, when they are compared with untreated population. Perhaps this mechanism has to be considered for breast cancers. On the other hand, postmenopausal women who take long-term replacement estrogen/progestagen therapy, have a better prognosis (with statistical significance) of breast or genital cancers occurred during the treatment, in comparision with untreated women.

According to Gornis and Denis[10] there is a possibility that distinctive progestagens have distinctive effects. Therapeutical use of progestagens is based on the pituitary-ovarial supression mechanism. It is not clear whether they are protective for breast cancer. If this is true, are there different mechanisms in their protective action on the mammary glandular cells and on the endometrial cells? They act on the endometrium by maintenance of low level of estrogen receptors with increase of 17-beta hydroxysteroid dehydrogenase activity.

Cahn and al[11] conducted a retrospective study of 156 female patients who had benign breast lesion. Fifty seven of them had a tissue biopsy which prelude further development of breast carcinoma, like sclerosanting adenosis, intraductal papilloma and atypical epithelial hyperplasia. Almost 63% of these 57 (v.s. 36 patients), recived hormonal replacement therapy (HRT). The other 99 out of total 157 patients had nonproliferative lesions. Thirty patients of them also recived HRT. From the results, the authors concluded that the use of HRT could cause development of lesions, leading to breast carinoma.

A special comparative study was done by Kaufman and al.[12] The data from 1686 selected patients were compared with 2077 hospital control cases, from which 1120 were with nongenital cancers and 957 with nonmalignant disease.The data were collected through interviews in the period from 1980 to 1986. The results from this study didn't prove proposition that the use of nonopponent conjugated estrogens could increase the risk for breast cancer, even if they have been used for a long period. This study is insufficient for evaluation of the effect of nonconjugated estrogen and combined estrogen/progestagen therapy.

The biggest published double blind control study (Nachtigall),[13] showed that the number of breast carcinomas among the users of HRT was lower than in the placebo group, with a statistical significance. The recent Nurses Health Cohort Study[14] showed a relatively increased risk (1,32) for breast carcinomas in users of estrogen HRT and 1,41 in combined estrogen/progestogen HRT users. Standford[15] reports decreased risk for breast carcinoma in patients treated with long-term combined HRT. During the estimation of the relationship between the consumption of progestogens and incidence of breast cancer, a significantly lower incidence of this cancer is found in France opposite to the USA.These facts could be explained with higher consumption of progestogens in a long period in all West European countries.

Li Ci and al[16] in their population-based case-control study of 975 women 65–79 years of age with invasive breast cancer and 1007 population control found that women using unopposed estrogen HRT even for 25 years or longer, had no appreciable increase in risk of breast cancer, but ever users of combined HRT(CHRT) had a 1,7-fold(95% CI) increased risk of invasive breast cancer, especially in those with longer durations.

Prolonged exposure to estrogens slightly increases the risk of breast cancer. Questions that so far not completely answered are as following: are estrogens tumor promotors and accelerators of the clinically occult pre-existing tumors or they are genotoxic mutagenic carcinogens which initiate tumors by way of accumulation of DNA-replication damage mechanism? The action of different progestogens on the estrogen-induced cellular mitosis could vary from the estrogen receptor downregulation, activating or stimulating apoptosis. It is not clear whether there is a difference in risk with sequentially combined versus continuously combined HRT. According to Eden,[17] although the recent Women's Health Initiative trial showed a small increase in the risk of invasive breast cancer in women undergoing therapy for 5 years or more, a clear consensus regarding the relationship between HRT and breast cancer risk cannot yet be drawn. Studies have consistently documented that HRT use is associated with improved mortality and survival rates for women with breast cancer. Large-scale, randomized studies on different progestin regimens are needed to critically assess the effect of progestin on breast cancer.

Conclusion

In our short-term study of the hormone replacement therapy with estrogens/progestogens in 35 post-menopausal women, the mammographic findings predominantly manifested the regression or stagnation of the breast changes.

A clear consensus regarding the relationship between HRT and breast cancer risk cannot yet be drawn.

Large scale, randomized studies on different progestogen regimens to assess its effect on breast changes are needed.

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