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The Treatment with Hormone Replacement Therapy and Phytoestrogens and The Evolution of Urogenital Symptoms in Postmenopausal Women

Bungau S[1], Tit DM[1]*, Fodor K[1] and Purza L[2]

[1]Department of Pharmacy, University of Oradea, Romania

[2]SC Biostandard 2007 SRL, Romania

***Corresponding Author:** Delia Mirela Țiț, Department of Pharmacy, Faculty of Medicine and Pharmacy, University of Oradea, 29, N. Jiga St., 410028, Oradea, Romania.

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Abstract

The present study aims to optimize the treatment in menopause by replacing pharmaceutical preparations containing estroprogestatives with products containing phytoestrogens, with less contraindications and side effects. The objective of the study was to compare the *in vivo* effects of hormone therapy administered in small doses, with that of soy phytoestrogens, in the evolution of urogenital symptoms in postmenopausal women. The study represents a clinical-statistical research, conducted on 326 patients clinically diagnosed in post menopause with urogenital symptoms that have not been previously treated with hormone replacement therapy (HRT) or phytoestrogens. The patients were divided into three groups of which two with therapy: the first group received treatment in doses of 1 mg estradiol and 0.5 mg norethisterone acetate (NETA) p.o. daily (group of HRT); the second group - received an extract standardized at 40% containing 20 mg pure isoflavones (Genistein, Daidzein and Gliciteina) 40 mg p.o. daily (group of phytoestrogens) and a control group without therapy.

Symptom assessment was performed with a specific instrument, respectively a standardized questionnaire Menopause Rating Scale (MRS) initially at 6 months and at 12 months, after treatment initiation. It was found an improvement, statistically significant for all symptoms assessed both at 6 months and at 12 months - at the 2 treatment groups compared to the control group, without significant differences between the groups with therapy.

The study results are favorable evidence for the use of phytoestrogens derived from soy in the treatment of urogenital symptoms in postmenopausal women.

Keywords: *Menopause; Urogenital symptoms; Hormone replacement therapy; Phytoestrogens*

Abbreviations: HRT: Hormone Replacement Therapy; MRS: Menopause Rating Scale; NETA: Norethisterone Acetate; CDC: Center of Disease Control and Prevention;

Introduction

Depriving the body of estrogen due to the menopause causes symptomatic, histological and functional urogenital changes. These changes produce specific urogenital problems, including the urgent need to urinate, urinary incontinence, recurrent urinary tract infections [1] and discomfort symptoms, such as vaginal dryness and sexual dysfunction [2]. Along with the hot flashes and sleep disorders, vaginal dryness is considered a typical symptom of menopause [3-7], which is reported by 25% of women in the first year post menopause and their percentage increases to 47% in the third year post menopause [8]. Estrogen hormone therapy local or systemic significantly reduces the symptoms caused by urogenital atrophy [9]. However, systemic estrogen therapy is contraindicated for some women as it is associated with many risks (venothrombotic diseases, breast cancer, stroke and coronary disease) and imposes the need to assess

the benefits against the potential risks of the treatment [10]. According to recent studies HRT is administered in the lowest dose and for the shortest period necessary for symptom control [10]; with the reassessment of the need to continue hormone therapy at intervals of 6-12 months [11].

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The present study aims to optimize the treatment of postmenopausal urogenital symptoms by replacing estroprogestative pharmaceutical preparations, with preparations containing phytoestrogens, with less contraindications and side effects. Thus the aim of this study was to compare the *in vivo* effectiveness of low-dose HRT and of phytoestrogens in improving urogenital symptoms in postmenopausal women.

Material and Methods

The study was conducted over a period of 12 months, on three parallel groups, on a total of 326 women with characteristic menopausal symptoms of mild to severe intensity. Menopausal status at recruitment into the study, according to menstrual history, was the postmenopausal with definitive cessation of the cycle, naturally for at least 12 months and no more than 5 years for all patients.

Inclusion criteria: natural menopausal women with specific symptoms, mild to severe; minimum one year and maximum 5 years of menopause; without hormonal therapy.

Exclusion criteria: induced menopause; hormonal therapy; onset of menopause for more than 5 years; patients with concomitant illness that would contraindicate HRT;

In the statistical processing entered 326 women divided into three study groups as follows: group I - 96 patients receiving hormone replacement therapy (1 mg estradiol and 0.5 mg norethisterone acetate (NETA) po daily); group II - 124 patients with phytoestrogens (extract standardized at 40%, containing 20 mg of pure isoflavones (Genistein, Daidzein and Gliciteina) 40 mg po daily); group III - control, 106 patients, who have not received any kind of treatment.

Isoflavones extract was purchased from pharmacies/natural food store in the form of capsules, manufactured by Organika Canada or IPRAD-France, and the dose administrated was established together with the doctor, taking into account the indications of the prospectus.

The division into groups of patients was made according to the historic, evaluation and diagnosis, risks and benefits of the proposed treatment.

Statistical analysis was done by using the EPIINFO, version 6.0, a program of the Center for Disease Control and Prevention - CDC (Center of Disease Control and Prevention) in Atlanta, adapted to processing from medical statistics. We calculated average parameters, frequency ranges, standard deviations, tests of statistical significance by the Student method (t test) and χ^2. The distribution of tests is similar to the normal one, being used by hypotheses involving numerical data. *The t test* also called *Student test* takes into account the standard deviation of the sample.

Each patient included in the study was drawn up an informed consent form.

Evaluation was performed with a specific instrument Menopause Rating Scale (MRS), designed and standardized as a tool for self-assessment to evaluate symptoms/manifestations related to aging, under different conditions, of some groups of women; assessing symptom severity over time; assessing pre and post replacement therapy changes in menopause [14].

This is comprised of 11 items, divided into three areas: somatic-vegetative, psychological and urogenital. On the urogenital field are evaluated: bladder problems (urinating difficulty, urinating often, having trouble to refrain from urinating); vaginal dryness (dryness or burning sensation in the vagina, difficulty in having intercourse) and sexual problems (changes in sexual desire, sexual activity and satisfaction).

The evaluation of the completed questionnaire follows a simple scheme. The score increases point by point with the increase of symptom severity, perceived subjectively, for each of the 11 items (severity is expressed from 0 to 4 points for each item). By completing the five possible boxes of "severity" for each item, the respondent gives his personal perception. MRS total score ranges from 0 (asymptomatic) to 44 (most severe symptoms). Scores minimum /maximum when urogenital symptoms varies between 0-12 points (three symptoms: sexual problems, urinary problems, vaginal dryness), and the total score is based on summing the scores for each item in the field [14,15] .

Results and Discussion

The initial distribution of cases according with the severity of the symptoms does not interfere with the results. Initially there were no significant differences between the three groups in terms of uro-genital symptoms (p = 0.782). In all three groups predominated the patients with moderate or severe symptoms, regardless of the type of symptoms (table 1). The comparative results on the evolution of the evaluated urogenital symptoms at 6 and at 12 months are shown in Table 2.

Initial Symptoms Urogenital Symptoms	Phytotherapy Group		Hormone Therapy Group		Control Group	
	No.	%	No.	%	No.	%
Mild	24	19,35	17	17,89	20	18,87
Moderate	46	37,10	37	38,95	42	39,62
Severe	54	43,55	41	43,16	44	41,51

Table 1: *Distribution of cases according to the severity of initial symptoms.*

Sexual Problems

At 6 months, the disappearance of sexual problems was recorded at 28.23% in the group with phytotherapy, percentage insignificantly lower than the HRT group (31.58%) (p = 0.471), and significantly higher than the control group (19.81%) (p = 0.35).

In the control group, the disappearance of sexual problems was recorded at a percentage significantly lower than in the group with hormone therapy (19.81% vs 31.58%) (p = 0.003). Both in the phytoestrogens and in the THS group were recorded cases of worsening of the sexual problems (0.81% and 2.11%).

At 12 months, the disappearance of sexual problems was recorded at 33.06% in the group with phytotherapy, percentage insignificantly lower than the hormone therapy group (36.84%) (p = 0.433), and slightly higher than the control group (30.19%) (p = 0.532). At the control group the disappearance of sexual problems was recorded at a percentage insignificantly lower than the hormone therapy group (30.19% vs 36.84%) (p = 0.147). Both in the group with phytoestrogens and in the one with the hormone therapy were registered cases of worsening of the sexual problems at 12 months (0.81% and 2.11%).

Problems with the bladder

At 6 months, the disappearance of the bladder problems was recorded at 21.77% in the group with phytotherapy, percentage insignificantly lower than the hormone therapy group (24.21%) (p = 0.569), and slightly higher than the control group (17.92%) (p = 0.315). In the control group, the disappearance of the bladder problems was recorded at a percentage significantly lower than in the group with hormone therapy (17.92% vs 24.21%) (p = 0.101). In all the three groups were registered cases of worsening of the bladder problems (4.03%, 4.21% respectively 2.83%).

The evolution of urogenital symptoms	Phytotherapy Group				Hormone Therapy Group				Control Group			
	At 6 months		At 12 months		At 6 months		At 12 months		At 6 months		At 12 months	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Sexual Problems												
Absent	35	28,23	41	33,06	30	31,58	35	36,84	21	19,81	32	30,19
Ameliorated	17	13,71	32	25,81	11	11,58	22	23,16	15	14,15	14	13,21
Stationary	71	57,26	50	40,32	52	54,74	36	37,89	70	66,04	60	56,60
Worsened	1	0,81	1	0,81	2	2,11	2	2,11				
Urinary Symptoms												
Absent	27	21,77	38	30,65	23	24,21	33	34,74	19	17,92	31	29,25
Ameliorated	17	13,71	28	22,58	12	12,63	20	21,05	7	6,60	8	7,55
Stationary	75	60,48	54	43,55	56	58,95	38	40,00	77	72,64	62	58,49
Worsened	5	4,03	4	3,23	4	4,21	4	4,21	3	2,83	5	4,72
Vaginal Dryness												
Absent	42	33,87	51	41,13	36	37,89	42	44,21	23	21,70	39	36,79
Ameliorated	22	17,74	32	25,81	16	16,84	24	25,26	21	19,81	16	15,09
Stationary	60	48,39	41	33,06	40	42,11	26	27,37	60	56,60	49	46,23
Worsened					3	3,16	3	3,16	2	1,89	2	1,89

Table 2: *The evolution of urogenital symptoms on items.*

At 12 months, the disappearance of the bladder problems was registered at 30.65% in the group with phytotherapy, percentage insignificantly lower than of the hormone therapy group (34.74%) ($p = 0.390$), and slightly higher than of the control group (29.25%) ($p = 0.758$). In the control group, the disappearance of the bladder problems was registered at a percentage insignificantly lower than in the hormone therapy group (29.25% vs 34.74%) ($p = 0.227$). In all three groups were registered cases of worsening of the bladder problems (3.23%, 4.21% and 4.72%).

Vaginal Dryness

At 6 months, the disappearance of the vaginal dryness was registered at 33.87% of the group with phytotherapy, percentage insignificantly lower than of the hormone therapy group (37.89%) ($p = 0.407$), and significantly higher of the control group (21.70%) ($p = 0.003$). At the control group, the disappearance of the vaginal dryness was registered at a percentage significantly lower than in the group with hormone therapy (21.70% vs 37.89%) ($p < 0.001$). In the groups with hormone therapy in the control group were registered cases of worsening of the vaginal dryness (3.16% and 1.89%).

At 12 months, the disappearance of the vaginal dryness was registered at 41.13% in the group with phytotherapy, percentage insignificantly lower than of the hormone therapy group (44.21%) ($p = 0.535$), and slightly higher than of the control group (36.79%) ($p = 0.368$). At the control group, the disappearance of the vaginal dryness was registered at a percentage slightly lower than in the group with hormone therapy (36.79% vs 41.13%) ($p = 0.124$). And at 12 months were registered cases of vaginal dryness worsening in the group with hormone therapy and in the control group (3.16% and 1.89%).

Regardless of the group favorable development (symptom disappearance or improvement) was recorded especially for the vaginal dryness item:

a. At 6 months - 51.61% (33.87% absent, 17.74 ameliorated) in the group with phytotherapy, 54.74% (37.89% absent, 16.84% ameliorated) in the hormonotherapy group and 41.51% (21.70% absent, 19.81% ameliorated) in the control group;
b. At 12 months- 66.94% (41.13% absent, 25.81% ameliorated) in the group with phytotherapy, 69.47% (44.21% absent, 25.26% ameliorated) in hormonotherapy group and 51.88% (36.79% absent, 15.09% ameliorated) in the control group, followed by sexual problems:
c. At 6 months - 41.94% (28.23% absent, 13.71% ameliorated) in the group with phytotherapy, 43.16% (31.58% absent, 11.58% ameliorated) in the hormonotherapy group and 33.96% (19.81% absent, 14.15% ameliorated) in the control group;
d. At 12 months - 58.87% (33.06% absent, 25.81% ameliorated) in the group with phytotherapy, 60.00% (36.84% absent, 23.16% ameliorated) in the hormonotherapy group and 43.40% (30.19% absent, 13.21% ameliorated) in the control group.

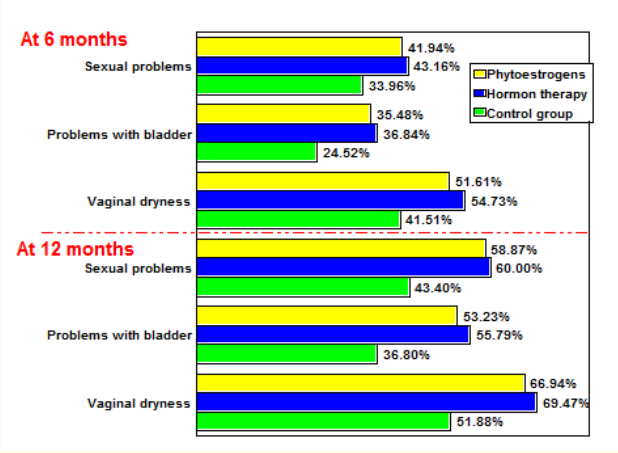

Figure 1: *The favorable evolution of the types of urogenital symptoms.*

The significantly higher percentage of patients with stationary symptoms in the control group compared to the 2 groups (45.28% vs. 25.00% respectively 27.37%) indicates a significantly better evolution ($p < 0.001$) in the groups with phytoestrogens and hormonotherapy.

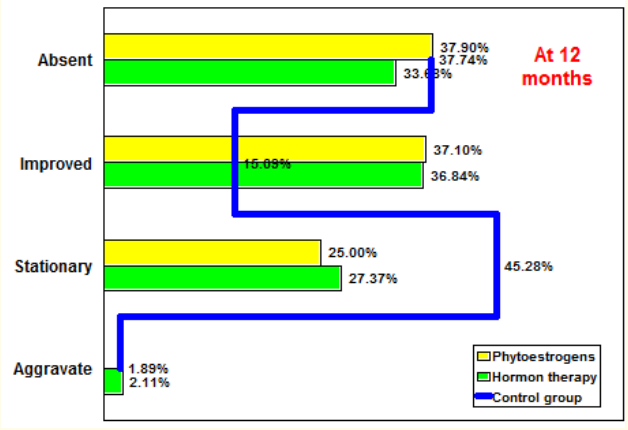

Figure 2: *Evolution of the urogenital symptoms.*

The unfavorable evolution of the symptomatology (worsening) occurred in a small percentage of the patients and was determined by the individual response to administered treatment. Further investigations in this case, did not identify other pathologies.

Both the phytoestrogen therapy and the hormone replacement therapy had a beneficial effect on the three groups of symptoms.

The best results, both in the group with HRT and in the phytoestrogen group were observed at 12 months after starting the treatment. It was also found that the hormonal treatment had slightly higher efficiency than phytoestrogens, which is consistent with data from other studies [15-19], but these differences were not statistically significant.

The advantages of this study model involves the possibility of choosing the type of therapy based on the individual risks and the choice of the patients, as well as using non-invasive evaluation methods, with efficient possibilities of comparing the results. It also allows the identification of the symptoms that respond best to the treatment administered.

The symptomatology assessment was based on the subjective perception of each patient included in the study; corroborating these data with gynecological examination, to determine the changes in the urogenital tract after treatment, would be welcome.

Conclusions

Specific urogenital symptoms contained in MRS assessment instruments used in this study responded well to both therapies, with no significant differences in the effectiveness of HRT therapy to phytoestrogens. Comparative analysis of the groups indicates that phytoestrogens and hormone therapy facilitates the disappearance or improvement of the assessed symptoms. The greatest impact of phytoestrogens and hormonal therapy was recorded on symptoms related to vaginal dryness, followed by sexual problems. The results of this study are a favorable evidence for the use of phytoestrogens derived from soy in the treatment of urogenital symptoms in postmenopausal women.

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