

## Soy isoflavones, lactobacilli, vitamin D<sub>3</sub> and calcium. Observational study in menopause

A.P. CAPUTI<sup>1</sup>, V. ARCORACI<sup>1</sup>, C. BENVENUTI<sup>2</sup>, ESTRONET STUDY GROUP\*

**SUMMARY: Soy isoflavones, lactobacilli, vitamin D<sub>3</sub> and calcium. Observational study in menopause.**

A.P. CAPUTI, V. ARCORACI, C. BENVENUTI, ESTRONET STUDY GROUP

*An observational study in clinical practice was carried out to draw an updated profile on the actual trend in menopause management and to detect the clinical activity of a new phytoestrogen. Each gynaecologist observed up to 10 consecutive menopause women, and collected the data concerning history, life style, past and actual treatments, HRT refusal/withdrawal, current therapy, symptoms, visits/exams in the previous 3 months, through the website www.estronet.net, by a confidential and protected individual access.*

*The 181 gynaecologists collected a sample of 1398 menopause women of which 607 not treated, 327 on estrogens, and 464 on phytoestrogens. The most used phytoestrogen in the study (87.1%) contains genistin and daidzin (30+30 mg) + lactobacilli, Ca and vit. D<sub>3</sub> (Estromineral, EM) and was administered to 392 women (aged 54.1 years, BMI 24.8) for 112.9 days (mean) up to 1 year. Menopause symptoms improved on EM independently from their baseline severity and the improvement increased with treatment duration: flushing improved up to 96.2% at 1 year; nocturnal sweating 100%, palpitations 63.6%, and vaginal dryness 56%.*

*Tumour fear, absence of symptoms and fear of weight gain were the most frequent reasons for refusal/withdrawal of HRT. Women treated (HRT or phytoestrogens) were more controlled both before and during the treatment. In presence of concomitant clinical conditions, EM was preferred. Phytoestrogens plus lactobacilli and mineral supplement showed a satisfactory clinical activity and safety.*

**RIASSUNTO: Isoflavoni di soia, lattobacilli, vitamina D<sub>3</sub> e calcio. Studio osservazionale in menopausa.**

A.P. CAPUTI, V. ARCORACI, C. BENVENUTI, ESTRONET STUDY GROUP

*Nel presente studio clinico osservazionale si sono valutati, nella pratica clinica quotidiana l'orientamento del ginecologo nella gestione della menopausa e l'attività clinica di uno specifico fitoestrogeno. Anamnesi, stile di vita, interruzione o rifiuto della terapia ormonale sostitutiva, trattamenti, patologie e terapie concomitanti, sintomatologia, visite e accertamenti nell'arco dell'ultimo trimestre, sono stati raccolti da 181 ginecologi italiani mediante il sito internet www.estronet.net con accesso individuale riservato e protetto.*

*Sono state analizzate 1398 donne in menopausa di cui 607 non trattate, 327 trattate con estrogeni e 464 con fitoestrogeni. Il fitoestrogeno più utilizzato nello studio (87.1%) conteneva genistina e daidzina (30+30 mg) + lattobacilli, Ca e vit. D<sub>3</sub> (Estromineral - EM) ed è stato somministrato a 392 donne (età 54.1 anni, BMI 24.8) per 112.9 giorni (in media) fino a 1 anno. I sintomi menopausali dopo trattamento con EM sono migliorati indipendentemente dalla loro gravità iniziale e il miglioramento era correlato alla durata del trattamento: a 1 anno le vampate sono migliorate fino al 96.2%, la sudorazione notturna al 100%, le palpitazioni al 63.6%, e la secchezza vaginale al 56%. Paura di neoplasie, assenza di sintomi e paura di aumentare di peso sono i motivi più frequenti di rifiuto della HRT. Le donne trattate (con HRT o fitoestrogeni) sono sottoposte a maggiori controlli clinici, prima e durante il trattamento. Con patologie concomitanti, il fitoestrogeno più scelto è stato EM, che ha mostrato una soddisfacente attività clinica e sicurezza.*

KEY WORDS: Phytoestrogens - Isoflavones - Menopause management.  
Fitoestrogeni - Isoflavoni - Menopausa.

## Introduction

Recent scientific acquisitions and regional differences in pharmacological approach have remodelled the prescription attitude in menopause (1, 2).

<sup>1</sup>University of Messina  
Clinical and Experimental Dept. of Medicine and Pharmacology,  
<sup>2</sup>Medical Dept. Rottapharm, Monza, Italy

Absolute and relative contraindications of hormone replacement therapy (HRT) are well known, being the risks of HRT represented by venous thromboembolism, gallbladder stones, mammary tumour and endometrial cancer.

On the other hand, it's also true that there is no standard therapy suitable for all menopausal women, as HRT is just a definition referred to different schemes appropriate for specific age and clinical condition (3). In fact, HRT is a valid and safe treatment

for moderate/severe acute vasomotor symptoms and vulvo-vaginal atrophy, provided its prescription is personalized HRT as doses, types, routes of administration, and combination, to optimize the benefits and reduce the risks.

Moreover, postmenopausal estrogen use is associated with osteoporosis prevention and, possibly, with a lower cardiovascular disease risk. Notwithstanding these sure benefits, long term compliance with estrogens is poor mainly due to patient concerns over cancer risk (4).

Furthermore, postmenopausal women who use estrogen combined with progestins (to prevent endometrial cancer) experience side effects such as vaginal bleeding (5).

These considerations pushed doctors and women to find alternatives whose definite effectiveness is still under investigation.

The start to a new menopause approach rose from the observation that osteoporosis, arteriosclerosis, breast and uterus tumours are less frequent in some oriental populations. Chinese and Japanese women more rarely complain menopause disturbs, as flushing, vaginal dryness and tissue atrophy of genital apparatus. These epidemiological data were attributed to alimentary habits of these populations, particularly to the great use of soy, whose seeds contain isoflavones, non steroidal substances with structure and action similar to estrogens. Isoflavones found in high concentrations in soy seeds are genistin and daidzin that belong to phytoestrogens family and show selective binding to estrogen receptor sites with weak estrogenic effects due to the mixed estrogen agonist and antagonist properties (6-8). They stimulate the production of Sex Hormone Binding Globulin and show a small but significant increase in plasma SHBG. This can explain their estrogenic antagonistic effect (9, 10), which confers them a role of natural selective estrogen receptor modulators with the potential of beneficial effects of ERT avoiding the most undesired estrogenic effects (11, 12).

In postmenopausal women consuming a phytoe-

strogen-rich diet, hot flushes and vaginal dryness were reduced and bone mineral density was increased (13). Phytoestrogens play a role in preventing cardiovascular disease and certain types of hormonally responsive cancers, as suggested by the data in Asian populations with high soy consumers (9, 10, 14, 15).

As endogenous estrogens have a central role in the aetiology of endometrial cancer (16), factors that alter endogenous oestrogen concentrations/expression, such as phytoestrogens and their agonist/antagonist action may positively influence the risk of the disease. On the other hand, in postmenopausal women, endogenous estrogen levels are very low, and phytoestrogens are more likely to bind to oestrogen receptors leading to biological effects (6, 17).

In fact Asian women show a lower incidence of endometrial cancer, in relation with the intake of soy food higher than the Western women (18). Asian populations consume 20–50 g of soy daily, which is their major source of phytoestrogens, comparable to a daily intake of 20–80 mg phytoestrogens (10). A confirmation of these data is given in a recent US survey, where isoflavones consumption was inversely related to the risk of endometrial cancer, even stronger in postmenopausal women (OR= 0.44, 95%CI= 0.26 to 0.77) (19). High intake of phytoestrogens in foods is uncommon in most Western countries.

A clinical pharmacology study demonstrated how the combination of isoflavones and estrogens reduces the estradiol-induced endometrial hyperplasia in menopause (20).

There are indications from observational studies that phytoestrogens protect against breast cancer (21-23). The Author's conclusions of a recent publication on phytoestrogens and breast cancer chemoprevention say that despite the present ambiguity, current data do suggest a potential benefit from use of phytoestrogens in breast cancer chemoprevention and therapy (24).

A project to draw an updated profile on the actual trend of Italian Gynaecologists in menopause

TABLE I - VITAL CHARACTERISTICS OF THE WOMEN STUDIED: NT NOT-TREATED, HERT ESTROGEN THERAPY, EM PHYTOESTROGENS (MEANS ± SD).

	NT	HERT	EM
Age (years)	55.5 ± 5.9	53.3 ± 5.0	54.1 ± 5.0
BMI (kg/m <sup>2</sup> )	24.6 ± 3.7	24.1 ± 3.2	24.8 ± 3.7
Systolic blood pressure (mmHg)	127.8 ± 13.6	126.5 ± 13.3	127.7 ± 13.9
Diastolic blood pressure (mmHg)	78.8 ± 8.3	77.9 ± 8.5	78.3 ± 9.4
Heart rate (beat/min)	76.7 ± 30.3	76.2 ± 7.7	75.0 ± 10.8

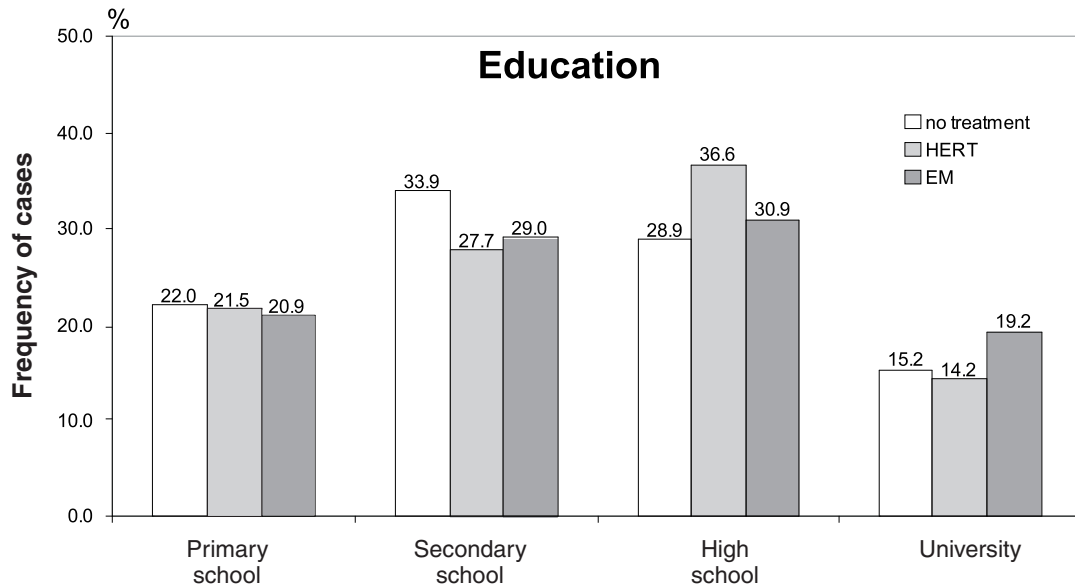


Fig. 1 - Education in the population studied.

management was designed. Moreover this study was taken as an opportunity to verify the acceptance and the clinical activity of a new phytoestrogen recently introduced in clinical practice, in which isoflavones are combined to lactobacillus sporogenes, vitamin D<sub>3</sub> and calcium. Lattobacilli were added to the formulation to supply glycosidase to the intestinal flora and so to guarantee the conversion of isoflavones in active aglyconic forms (genistein and daidzein, and the conversion of daidzin in the more active equol) (25).

## Methods

On an Internet based computerised procedure each gynaecologist observed up to 10 consecutive menopause women, whose data were recorded by an electronic case report form. Confidential access, protected by individual login and password allowed data input into the website [www.estro.net](http://www.estro.net) and data consultation by 181 gynaecologists.

History, life-style, past and actual treatments,

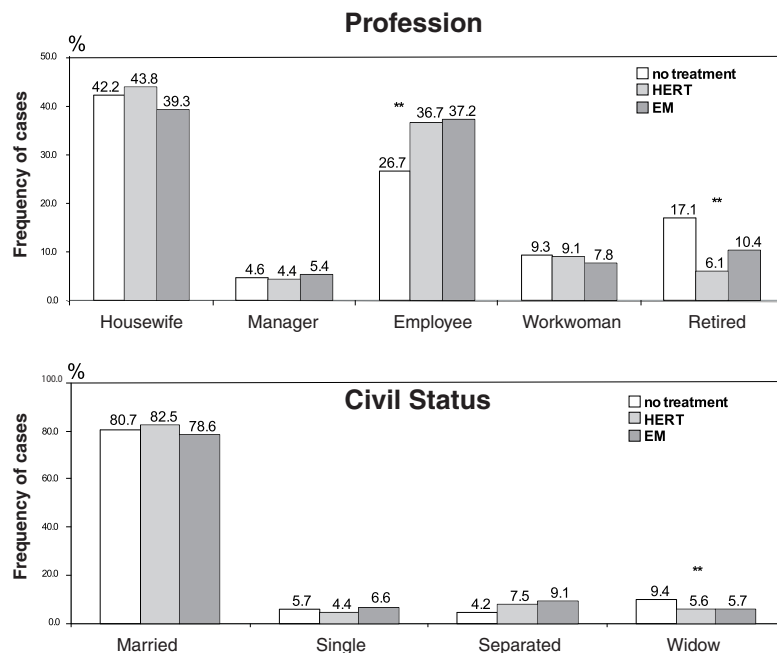


Fig. 2 - Profession and civil status of the women studied (\*\*p<0.01).

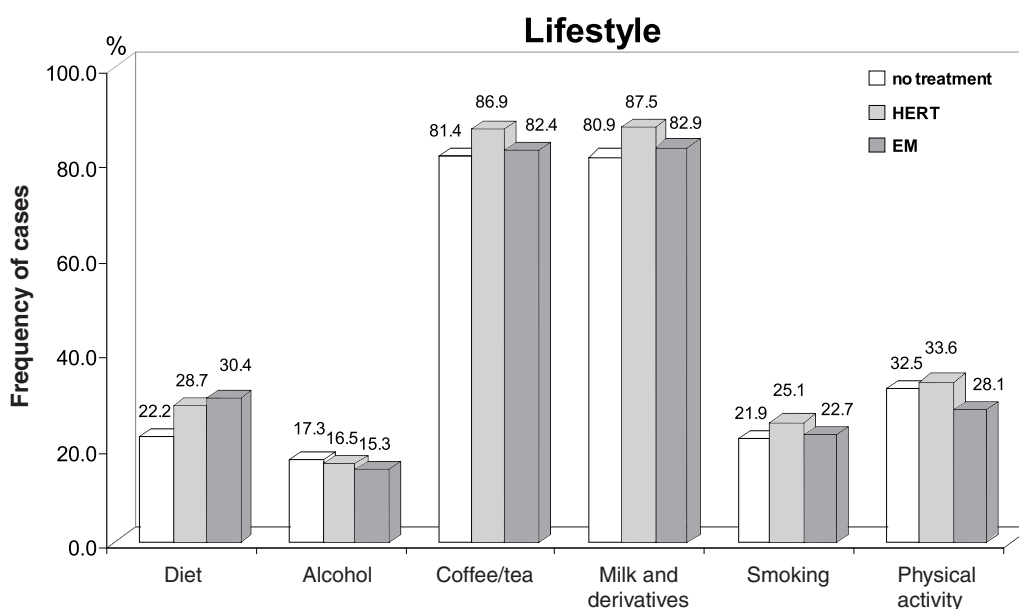


Fig. 3 - Lifestyle in the population studied.

HRT refusal/withdrawal, current pharmacological therapy, symptoms evaluation, visits/exams in the 3 months preceding the visit, were collected.

The characteristics of the not treated (NT), on hormone replacement therapy (HRT) and on phytoestrogens women were compared. Among the different phytoestrogens, the one combining genistin and daidzin (30+30 mg) + lactobacilli, Ca and vit D<sub>3</sub> [Estromineral, Rottapharm (EM)] was largely the most used in the study (87.1%), representing a

novelty for its composition.

A statistical description of the groups and their comparison by means of  $\chi^2$  square test were carried out when appropriate.

## Results

The study was carried out between May 2003 and June 2004 on 1398 menopause women (sponta-

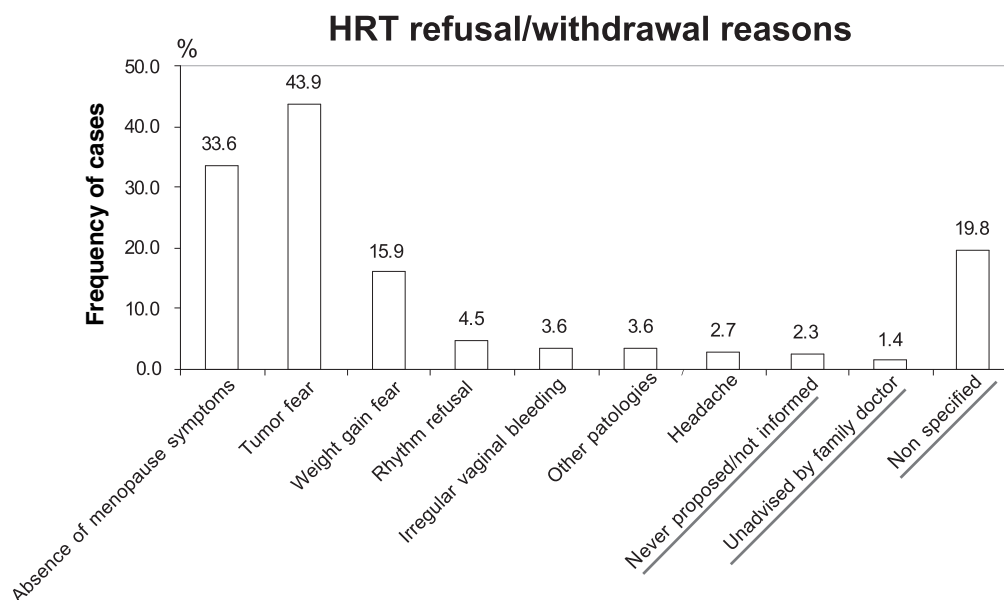


Fig. 4 - HRT refusal/withdrawal reasons in not-treated women.

neous 86.6% surgical 13.4%), of which 327 women (23.6%) were treated with Hormone (or Oestrogen) Replacement Therapy (HERT), 464 (33.5%) were on phytoestrogens and 607 (43.9%) received no specific treatment for menopause (NT). The estrogens used in HRT were represented by transdermal 64%, oral 18%, gel 12% and spray 6%; in 1.1% of the women they were administered in combination with phytoestrogens.

EM was administered to 392 women for a mean duration of 112.9 days.

The vital characteristics (mean ± SD) of the population were similar in the groups compared for age; blood pressure and heart rate (Tab. I).

The allocation to type of treatment showed no differences for Primary school Education, prevalence for NT for Secondary school, and for HERT and EM, respectively, in High school and University educated women (Fig. 1). Among professions, the employee

group chose/received more frequently an active treatment, while retired women preferred the non treatment (Fig. 2). No differences among groups for the civil status (Fig. 2).

Diet was more adopted by women on EM (30.4) and HERT (28.7%) than by NT (22.2%); while no clear differences rose for the others items of lifestyle considered (Fig. 3).

The more frequent reasons for HRT refusal or withdrawal were the tumour fear, the absence of menopause symptoms and a big area of non advised or non informed (Fig. 4).

Women treated (HERT or EM) underwent more exams both before and during the treatment than NT women (Fig. 5).

The most frequent concomitant pathological conditions were arthrosis, benign mammary diseases and hypertension, followed by osteoporosis (Fig. 6). The rates of EM users and NT women were higher than

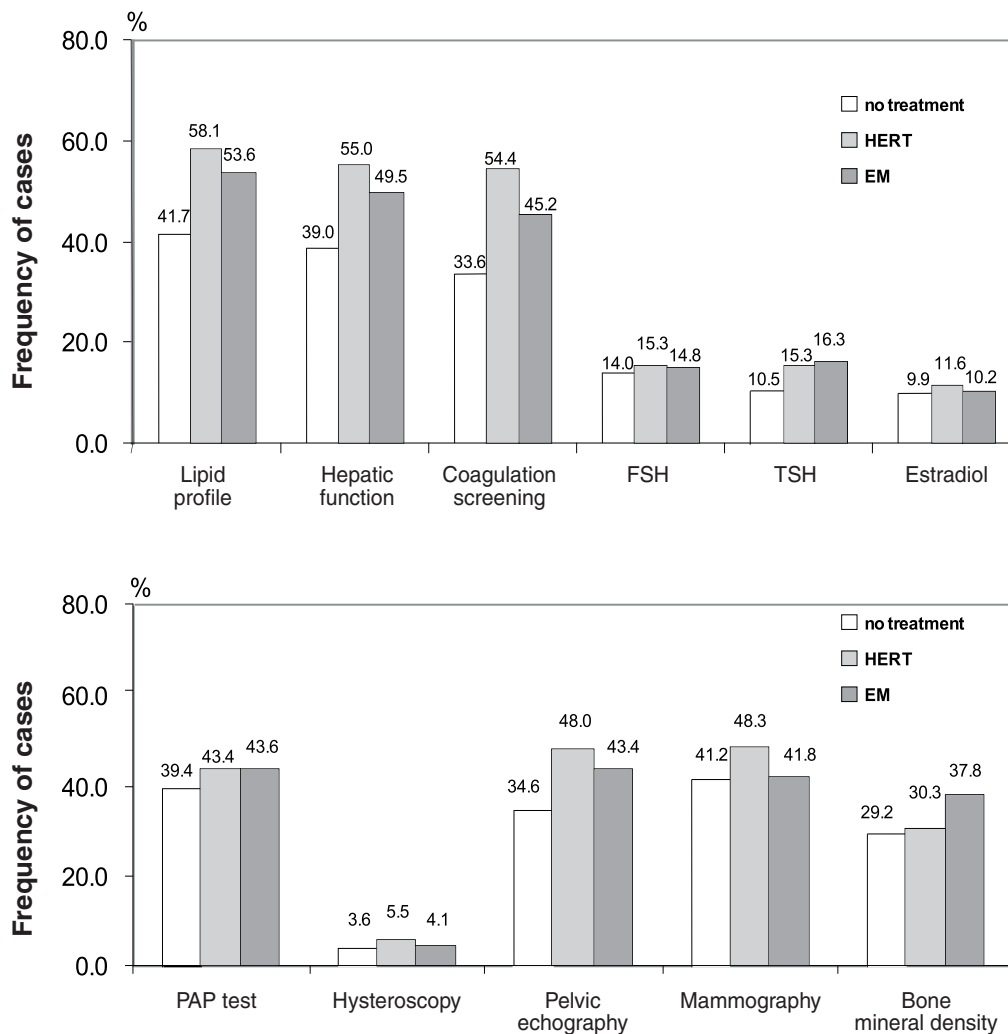


Fig. 5 - Exams carried out within the three months before the visit.

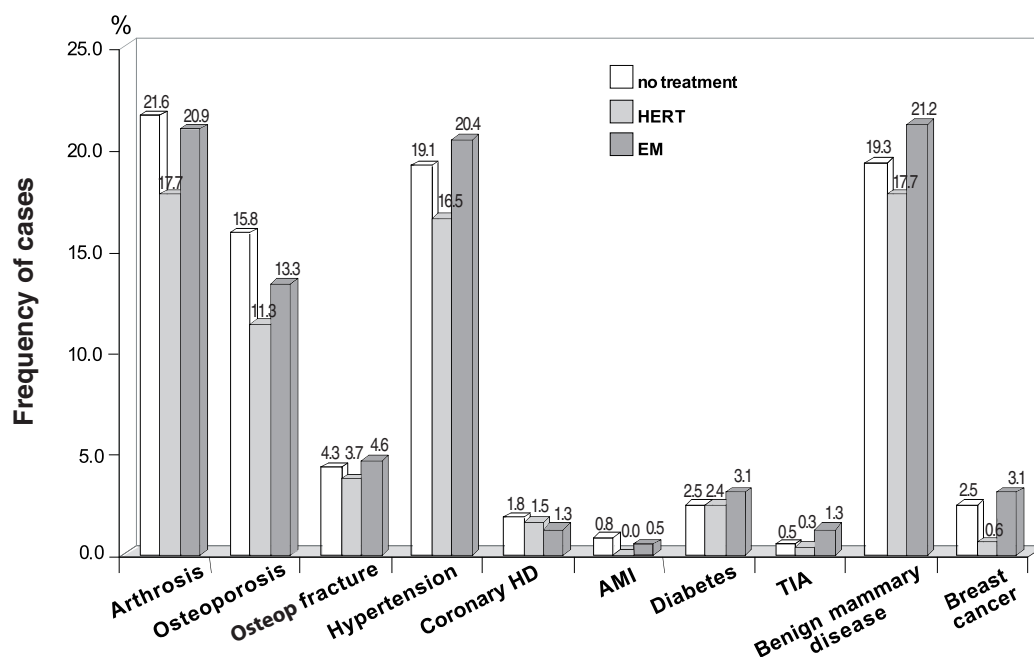


Fig. 6 - Clinical conditions concomitant to menopause.

HERT. When breast cancer was present, the treatment choice felt almost exclusively on EM or NT.

The most frequently concomitant therapies reported were calcium+vitamin D<sub>3</sub> and antihypertensive drugs (Fig. 7).

At start, the most present symptoms on EM treatment were flushing and nocturnal sweating (Fig. 8). The rate of EM responders was independent from the severity of menopause symptoms at start of EM treatment (Fig. 9). The clinical response to EM increased in relation with treatment duration (Fig. 10) and was

superior to the alternative phytoestrogen group, as flushing ( $p < 0.04$ ) and nocturnal sweating ( $p = 0.07$ ) were concerned (Fig. 11).

## Discussion

Women with a very low education (primary) trusted more in the gynaecologist advice and no difference among allocation to treatments was detected, a poor education (secondary) addressed

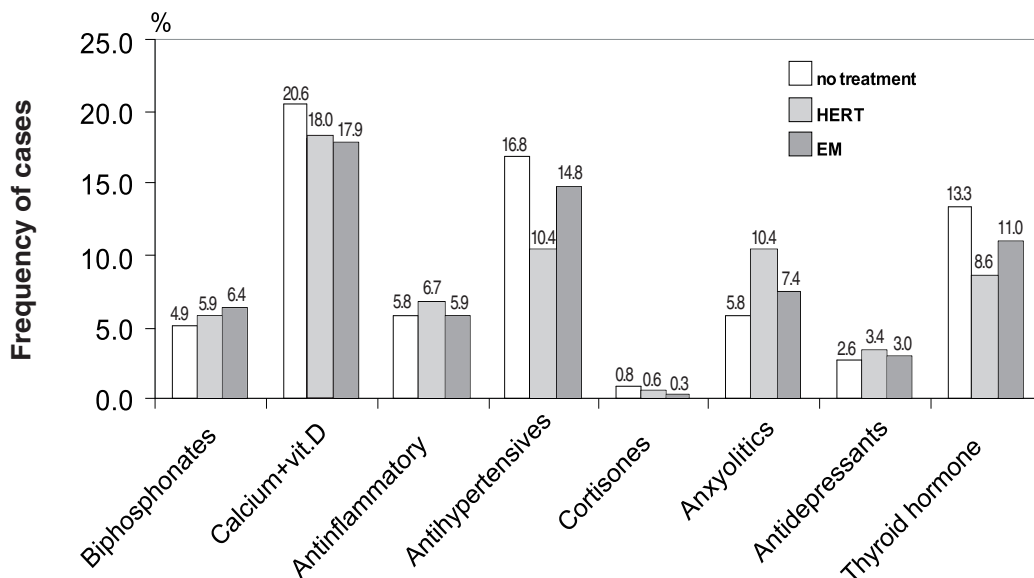


Fig. 7 - Concomitant therapies according to the stratification in menopause treatments.

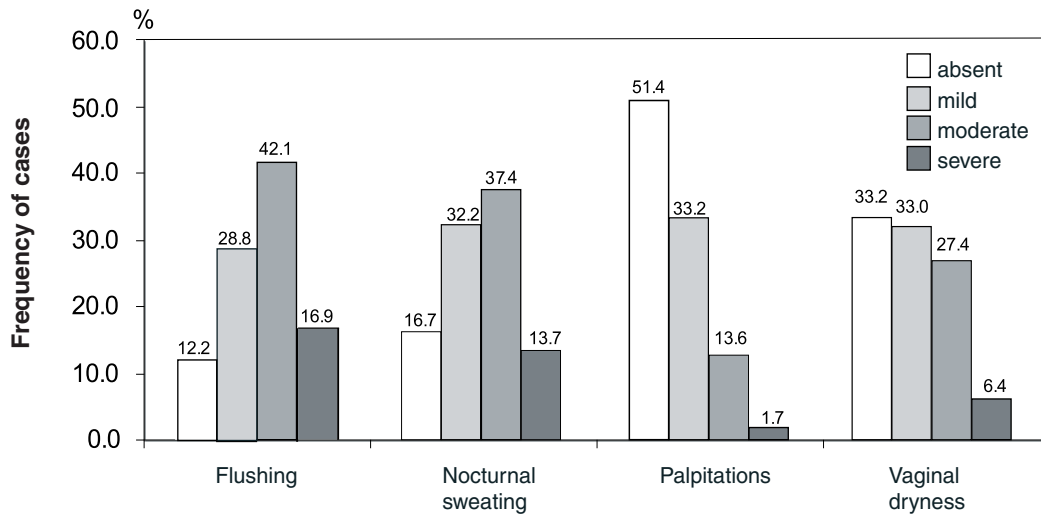


Fig. 8 - Severity of symptoms at start of EM treatment.

to a non treatment choice, and high education pushed to oestrogen treatment, while university formation favoured the decision to alternative therapies in response to doubts of safety.

Women who accept whatever a treatment, declared to be much more on diet than the non-treated, showing a higher interest for their fitness. In the mean time it can be observed that women compliant to HRT or phytoestrogens treatment are much more controlled than the not-treated.

Examining the different reasons to refuse or abandon HRT, it clearly appears that beside the fear of tumour, a very large sample of the population (globally more than 23%) manifested inac-

curate information (never proposed/not informed, unadvised by family doctor, or not even able to specify the reason). This outcome identifies the need for improving the communication towards the menopause women to increase their awareness of the risk and benefit of a correct approach.

In presence of concomitant pathological conditions, the rate of EM users was higher than HRT users and similar to NT incidence. When breast cancer was involved, the treatment choice felt almost exclusively on EM or NT.

Data on concomitant therapies show the compatibility of EM with different pharmacological classes.

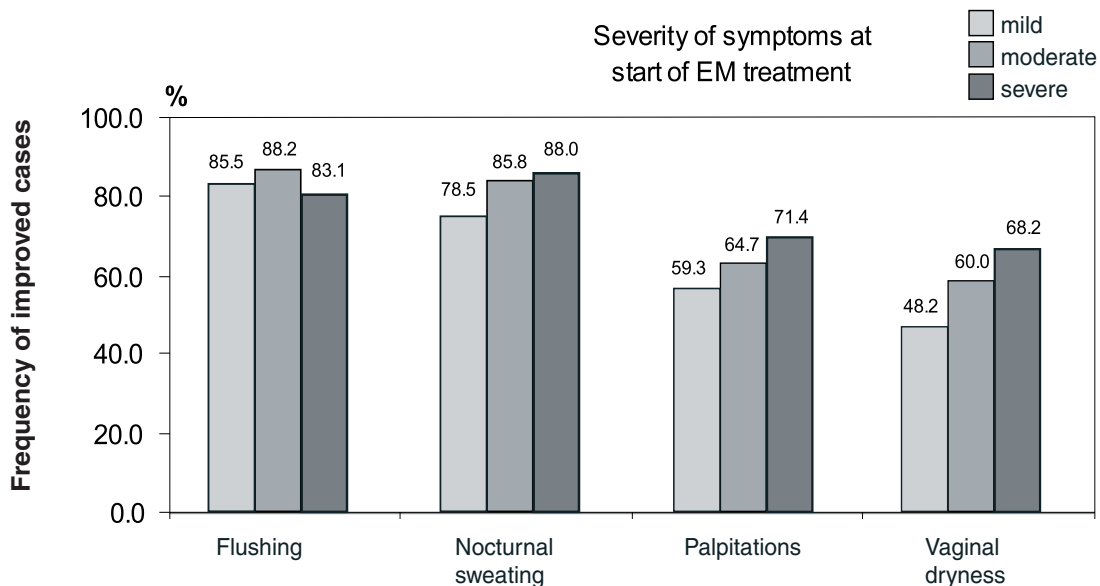


Fig. 9 - Clinical activity of EM according to the symptoms severity at EM start.

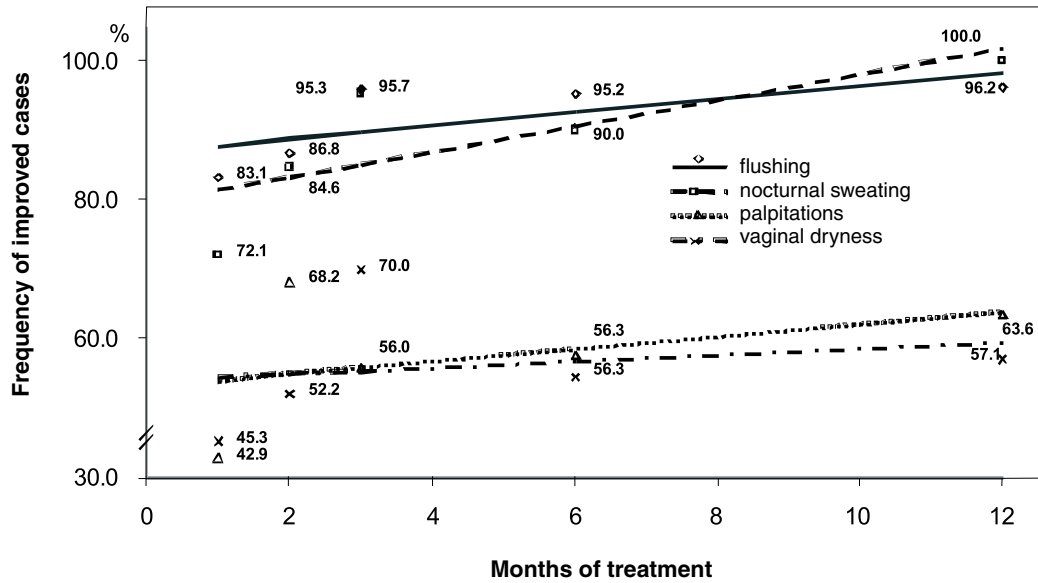


Fig. 10 - Clinical activity of EM according to the duration of EM treatment.

## Conclusions

This observational study confirmed the reasons for refusal/withdrawal of HRT.

Women treated (HRT or phytoestrogens) appear more controlled both before and during the treatment.

An opportunity to verify the clinical activity of a new phytoestrogen, in which isoflavones are com-

bined to lactobacilli, vitamin D<sub>3</sub> and calcium, in clinical practice.

In presence of concomitant clinical conditions, the natural approach with phytoestrogens is preferred.

Phytoestrogens plus lactobacilli and mineral supplement show a satisfactory clinical activity, correlated to duration of treatment and greater to the one of other phytoestrogens.

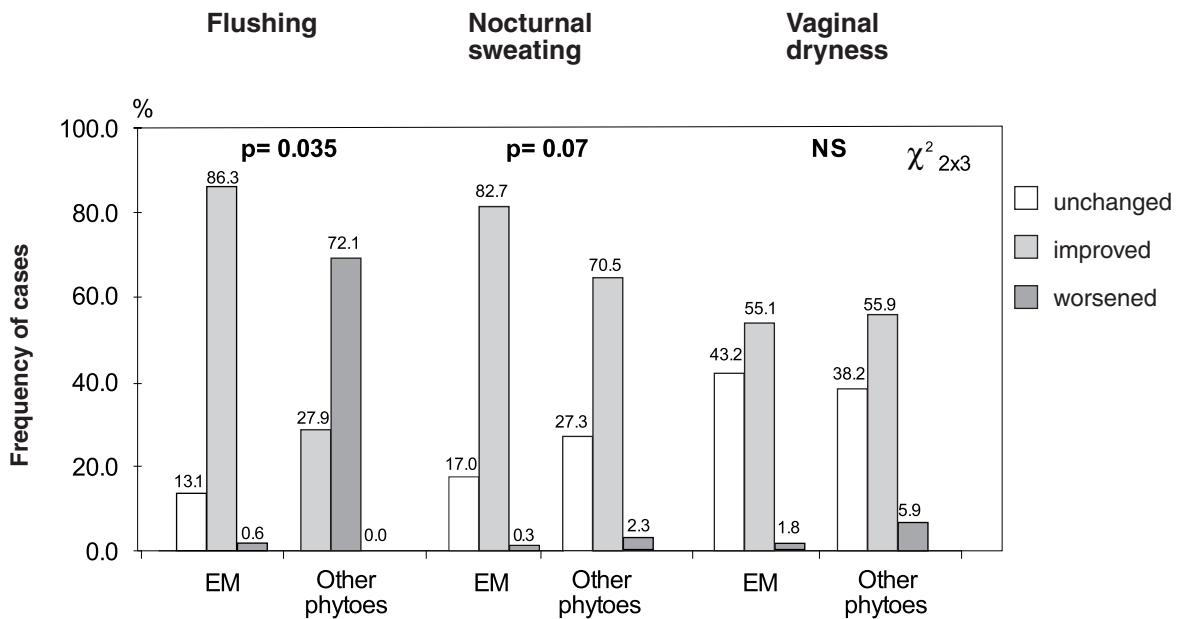


Fig. 11 - Comparative clinical activity between EM and other phytoestrogens.



**\*Estronet study group**

Agnello A., Padova; Agostinelli D., Bari; Albertin E., Ponte S. Nicolò (PD); Alio L., Palermo; Amato M. Teresa, Caltagirone (CT); Anelli R., Cusano Milanino (MI); Arienzo M., Napoli; Baj G., Novara; Baldaccini E., Alatri (FR); Baldini M., Loc. Quarto (PC); Barbadori M.A., Ancona; Barbaro M. Luisa, Messina; Bartolini T., Lucca; Battistella G., Teramo; Belsanti A., Andria; Benanti R., Palermo; Benatti G., Soliera (MO); Bergamaschi D., Mestre (VE); Bertocchi L., Bologna; Bianca M., Avola (SR); Biancheri D., Bordighera (IM); Bocconi L., Milano; Bolelli E., Bologna; Bordin G., Vicenza; Bori S., Perugia; Bray F., Melegnano (MI); Brun A., Pozzuoli; Cagnacci A., Modena; Calvisi L., Reggio Emilia; Campanelli T., Spoleto (PG); Carmina A., Palermo; Carrubba M., Caltanissetta; Cascio A., Casier (TV); Cascio N., Brescia; Caselli C., Siena; Cavanna L., Torino; Cazavacca R., Arezzo; Ceccarelli P., Lucca; Cerini M.R., Novara; Cerreoni A., Cesena; Chionna R., Palazzo P. (CR); Chirico C., Ferrara; Ciccone C., Avellino; Cirillo S., Parma; Colonnelli M., Perugia; Conti C., Fano (PU); Coppola C., Torino; Costabile L., Caserta; Cotardo R., Torino; Cuciniello A., Angri (SA); Cusmai R., Brescia; De Angelis P., Popoli; De Giorgi A., S. Cesario (LE); De Matthaes L., Mesagne (BR); De Troia L., Roma; Della Peruta S., Arona (NO); Di Natale R., Palermo; Dimaggio A., Francavilla Fontana (BR); Ercolano S., Castellammare di Stabia (NA); Favi O., Livorno; Ferruccio C., Mesagne (BR); Filippa N., Vigevano; Fiorillo F., Napoli; Fontanesi V., Albinea (RE); Franchi F., Siena; Frattini G., Fano (PU); Galantino P., Bari; Gallo M., Torino; Garofalo M., Cosenza; Gherardini D., Portice (MO); Giardina S., Foggia; Giorgino L.F., Padova; Gobbi F., Rivoli (TO); Gravina G., S. Severo (FG); Graziano R., Palermo; Guastaferrò L., Modena; Guidoni G.C., Siena; Izzo S., Benevento; La Moglia A., Napoli; Lentini G., Palermo; Leonardi M., Brescia; Levanti S., Pisa; Licata A., Enna; Loiudice L., Bari; Lucianetti M., Bergamo; Macri G., Locri (RC); Maestrini G., Firenze; Maggiorelli M., Pratolino (FI); Mancini A.C., Modena; Mancuso M., Salerno; Marchetto G., Treviso; Marcozzi S., Milano; Mariatti M., Orbassano; Martinelli

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