

## EVALUATION OF PHYTOESTROGENS AS A THERAPEUTIC ALTERNATIVE TO HORMONE REPLACEMENT THERAPY (HRT) IN POSTMENOPAUSAL WOMEN

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### ABSTRACT

#### BACKGROUND

Even in today's scenario, post-menopausal women are blindly treated with Hormone Replacement Therapy to alleviate the symptoms without proper judgment of its side effects. This study was carried to evaluate the role of phytoestrogens as a therapeutic alternative to Hormone Replacement therapy in post-menopausal women.

#### MATERIALS AND METHODS

This prospective study was carried in the Department of Obstetrics & Gynaecology, Rama Medical Collage Hospital & Research Centre, Mandhana, Kanpur, to evaluate the role of phytoestrogens as a therapeutic alternative to Hormone Replacement therapy in post-menopausal women, 90 symptomatic post-menopausal women with both natural and surgical menopause with symptoms related to menopausal syndrome were selected. All 90 selected post-menopausal women were administered with a regular dose of phytoestrogen namely soy Isoflavones for a period of 6 months. The cases were followed-up and severity of symptoms were studied regularly for a time of 6 months.

#### RESULTS

Out of 90 cases regular treatment was observed in 75 cases, while 6 cases took irregular treatment, 5 cases stopped treatment and 4 cases failed to follow up. All the 75 regular cases showed substantial improvement in symptoms like vasomotor symptoms, insomnia, depression, lethargy, etc. Maximum benefit was found in hot flushes, insomnia, depression, lethargy and vaginal dryness.

#### CONCLUSION

Though the results of our study was highly encouraging and comparable with earlier studies, the significant role of phytoestrogen over HRT cannot be fully established, but a repeated study over larger count of patients and increased duration of therapy can prove superior role of phytoestrogen over HRT, without any side effects.

#### KEYWORDS

Phytoestrogens, Hormone Replacement Therapy, Vasomotor Symptoms, Menopause.

**HOW TO CITE THIS ARTICLE:** Vithal S. Evaluation of phytoestrogens as a therapeutic alternative to hormone replacement therapy (HRT) in postmenopausal women. J. Evolution Med. Dent. Sci. 2016;5(103):7587-7591, DOI: 10.14260/jemds/2016/1716

#### BACKGROUND

Menopause is defined as a permanent cessation of menses for one year. It is a beginning of an era in the life of a woman, which is associated with physical, mental and psychological changes.<sup>(1)</sup>

Menopause is often associated with large number of troublesome symptoms like hot flushes, night sweats, insomnia, mood fluctuation, vaginal atrophy, urinary symptoms, repeated urinary tract infections (UTI), memory impairment, skin changes, weight gain, osteoporosis, cardiovascular diseases, etc.<sup>(2)</sup>

To relieve symptoms, Hormone Replacement Therapy (HRT) has been advocated for long. Though extremely beneficial, it has certain side effects and limitations, which include abnormal bleeding per vaginum, nausea, vomiting, headache, migraine, oedema, weight gain, derangement of carbohydrate and lipid metabolism.

Also, there is increased risk of carcinoma breast and carcinoma endometrium. It is also contraindicated in many conditions like uncontrolled hypertension, diabetes mellitus, active liver disease, history of thromboembolism, known coronary heart disease, migraine, endometrial hyperplasia, etc.<sup>(1)</sup>

In search of a safe agent in place of HRT, Selective Estrogen Receptor Modulators (SERMs) have been developed. Amongst them, phytoestrogens have emerged as a promising alternative to HRT. Phytoestrogens are plant-derived compounds that exert both estrogenic and antiestrogenic effects. There are seven classes of phytoestrogens out of which isoflavones are most commonly used.<sup>(2)</sup>

Most of the Indian postmenopausal women do not come forward for investigations and followup. Unsupervised HRT may be dangerous for our population. Phytoestrogens, though less effective are claimed to be devoid of complications and side effects. So for our population, phytoestrogens appear to be a promising alternative to HRT. Therefore, we planned to study the efficacy and side effects of phytoestrogens on symptomatic postmenopausal women.<sup>(3)</sup>

#### MATERIALS & METHODS

The present study was conducted over a period of 12 months from August 2015 to July 2016 in the Department of

*Financial or Other, Competing Interest: None.*

*Submission 20-11-2016, Peer Review 13-12-2016,*

*Acceptance 20-12-2016, Published 26-12-2016.*

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*DOI: 10.14260/jemds/2016/1716*



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### Selection of Patients

90 symptomatic post-menopausal women with both natural and surgical menopause with symptoms related to menopausal syndrome, coming to outpatient department were selected. All women were counselled about the various treatment options including HRT & phytoestrogens, advantages, limitations and side effects of HRT and phytoestrogens were explained to them and women who chose phytoestrogens were included in the study. (3,4,5,6)

### Inclusion Criteria

1. Symptomatic patients with natural menopause for at least one year.
2. Symptomatic patients with surgical menopause (Total Abdominal Hysterectomy with Bilateral Salpingo-oophorectomy) at least 3 months prior to entry.
3. Women who were unwilling or unsuitable for conventional HRT.

### Exclusion Criteria

1. Asymptomatic women.
2. Women not willing for treatment.
3. Women who cannot come for followup.
4. Women already taking HRT.
5. Undiagnosed genital bleeding.
6. Known or suspected malignancy.
7. Active infections (UTI, infective vaginitis/vulvitis, etc.).
8. Other acute medical/surgical illness.

### Study Procedure

An informed written consent was obtained from each patient after explaining them treatment pattern and follow-up schedule. Detailed medical and gynaecological history was obtained. Detailed general, systemic, breast, local and gynaecological examination and Pap smear was done in all cases and recorded in the worksheet. If any abnormality was found, the case was excluded from the study. All the women included in the study were prescribed 75 mg isoflavone once a day preferably with milk for a period of 6 months. (6,7)

### Symptoms were divided into Six Groups

1. Vasomotor- hot flushes, night sweats.
2. Psychological- insomnia, irritability, depression, lethargy.
3. Genital symptoms- vaginal dryness, vaginal irritation.
4. Sexual dysfunction- dyspareunia, loss of libido.
5. Musculoskeletal- muscle, bone and joint pains.
6. Urinary- burning, hesitancy, incontinence, frequency.

Symptoms were graded on a four-point scale according to severity. (8,9,10,11)

### Scale

- 0 - None  
1 - Mild  
2 - Moderate  
3 - Severe

### Investigations

Haemoglobin level, urine routine and microscopy, fasting and postprandial blood sugar, lipid profile and transvaginal sonography for endometrial thickness were done in all cases. If any abnormality detected, they were excluded from the study.

The findings were recorded in the format and all women were followed at 3 and 6 months. On each follow-up, they were assessed for-

- a) Symptom score.
- b) General examination.
- c) Breast examination.
- d) Gynaecological examination.
- e) Investigations- Lipid profile and transvaginal sonography- for endometrial thickness. (At the end of six months).

The results were obtained, observed and subjected to standard statistical analysis to reach a final outcome.

### RESULTS

There was significant decrease in hot flushes, lethargy, vaginal dryness and irritation, muscle bone and joint pains at 3 months. At six months, hot flushes, vaginal dryness and burning micturition further improved. Rest of symptoms were more or less the same as they were at 3 months. Increasing the duration of therapy did not help in improving all the symptoms but was beneficial in some. (12,13,14)

Symptoms	0 (Months)	3 (Months)	6 (Months)	P value at 6 Months
Vasomotor	67 (99.6%)	57 (69.3%)	52 (69.3%)	0.000
Insomnia	31 (41.3%)	29 (38.6%)	28 (37.3%)	0.103
Irritability	51 (68.1%)	49 (65.31%)	49 (65.3%)	0.567
Depression	11 (14.6%)	9 (12.0%)	7 (9.3%)	0.024
Lethargy	57 (76.0%)	47 (62.6%)	46 (61.3%)	0.001
Vaginal Dryness	47 (57.3%)	42 (45.3%)	37 (42.6%)	0.002
Hesitancy in Maturation	8 (10.3%)	6 (8.6%)	6 (8.6%)	0.321
Urinary Incontinence	16 (14.4%)	14 (10.56%)	14 (10.56%)	0.159
Frequency of Micturition	13 (18.10%)	9 (12.25%)	7 (10%)	0.024
Burning Micturition	32 (28.8%)	26 (19.5%)	24 (81.0%)	0.004
Sexual Dysfunction	45 (60.0%)	42 (56.0%)	42 (56.0%)	0.083
Muscle, Bone and Joint Pains	42 (56.0%)	35 (46.6%)	34 (45.3%)	0.002

**Table 1. Effect of Phytoestrogens on the Incidence of Post-menopausal Symptoms (In percentage) (n=75)**

Symptoms (Mean)	0 (Months)	3 (Months)	6 (Months)	P value at 6 Months
Vasomotor	2.1	1.6	1.1	0.000
Insomnia	0.89	0.75	0.49	0.000
Irritability	1.44	1.27	1.22	0.026
Depression	0.54	0.34	0.27	0.040
Lethargy	1.47	1.38	1.18	0.000
Vaginal Dryness Irritation	1.33	0.95	0.75	0.000
Hesitancy in Micturition	1.07	1.02	1.02	0.083
Urinary Incontinence	1.40	0.090	0.090	0.002
Frequency Micturition	1.50	1.01	0.08	0.015
Burning Micturition	2.08	1.90	1.75	0.000
Sexual Dysfunction	1.50	1.31	1.25	0.083
Muscle, Bone and Joint Pains	1.16	1.12	1.07	0.057

**Table 2. Effect of Phytoestrogens on the Severity of Post-menopausal Symptoms (n=75)**

At 3 months, there was significant decrease in the mean score of severity of vasomotor symptoms, insomnia, depression, lethargy, vaginal dryness and burning micturition. Severity score further decreased at 6 months in all symptoms except hesitancy and urinary incontinence. Maximum benefit was found in hot flushes, insomnia, depression, lethargy and vaginal dryness. Hence, prolonging therapy helps in reducing the severity of symptoms.

Side Effects	Number	Percentage
Bloating	07	9.0
Weight Gain	-	-
Nausea	-	-
Epigastria Pain	-	-
Oedema Hand & Feet	-	-
Breast Discomfort	-	-
Leg Cramps	-	-
Others	-	-

**Table 3. Side Effects of Phytoestrogens (n=75)**

No disturbing side effects were observed by any of the case. Only 9% women had minimal bloating which was acceptable to them. Most of the women were free from fear of long term complications like malignancy and weight gain. <sup>(15,16)</sup>

**DISCUSSION**

Recently, there has been a global effort to find alternative and natural treatments for menopause, so phytoestrogens prove as an attractive addition to the choices available for the treatment of postmenopausal syndrome. In our study, 90 postmenopausal cases with both surgical and natural menopause were given a phytoestrogen preparation to alleviate these symptoms and outcomes were studied for a period of six months.

- Drug was started in maximum number of cases with natural menopause for 1-2 years and with surgical menopause 1.5-2 years which was comparable.
- Compliance was less in our study. Out of 90 cases, 75 cases took regular treatments for six months, whereas 6 took irregularly, 5 cases stopped treatment on their own and loss to follow up was seen in 4 cases.
- The average figures of climacteric symptoms in the study by Shah et al were comparable to our study. Hot flushes in 86.2% irritability 69.2, depression 53.3%, insomnia 62.4%, sexual dysfunction 62.9%, vulval irritation and dryness 75.9% and urinary incontinence 60%, cases. Urinary incontinence and depression was less in our study.
- In our study, 75 mg isoflavone was prescribed per day for six months while Albert et al, gave 70 mg per day for 4 months, which was comparable to our study whereas Upmalis et al used a lower dose of 50 mg per day for six months in 177 women.
- The incidence of hot flushes decreased from 88.6% to 69.3% (20% reduction) at the end of six months which was highly significant (P=0.000) while the mean number of hot flushes decreased from 11.12 to 8.61 and the severity score decreased from 2.1 to 1.1 (P=0.000). Upmalis et al reported 25% reduction in the frequency and severity of hot flushes which was comparable to our study whereas study by Albertazzi et al showed a very high decrease in the number of hot flushes up to 1.59 fold.
- Insomnia decreased from 41.3% to 37.3% which was statistically not significant but the severity score decreased from 0.89 to 0.49 which was significant (P=0.000). Similar findings were given by Drew and Puk. Singh et al showed 83% improvement in the incidence of insomnia but there were only 29 women in their study, 169 in the study by Drew et al and 75 in our study.
- Psychological symptoms like irritability showed little improvement of 2.7% which was not statistically significant and severity score dropped from 1.44 to 1.22 (P=0.026) whereas Shah et al reported a significant reduction of 19%.
- The incidence of depression dropped from 11% to 7% and severity score from 0.54 to 0.27 which was not statistically significant while the study by Shah et al showed 43% improvement.
- The incidence of lethargy decreased from 76% to 61% and severity score 1.47 to 1.18 (P= 0.000) which was highly significant. Shah et al also showed similar findings.
- In our studies, there was decrease in the incidence of vaginal dryness and irritation from 47% to 37% and severity score from 1.33 to 0.75 (P=0.000) which was highly significant and the findings were comparable to study by Han et al.
- The incidence of sexual dysfunction (loss of libido and dyspareunia) decreased from 45% to 42% while the severity dropped from 1.51 to 1.25 which was not significant as many of the cases were not sexually active or widows.
- There was decrease in the incidence of urinary symptoms but were statistically not significant.

- The incidence of muscle, bone and joint pains dropped from 56% to 45.3% (P= 0.002) which was statistically significant and the severity dropped from 1.16 to 1.07. These findings were similar to Singh et al.
- The overall improvement in the menopausal symptoms observed in the present study were consistent with the finding of Murkies et al, who reported decrease in symptom score of hot flushes, sleep disturbance, depression, tiredness, irritability and urogenital symptoms.
- Also, there was no significant variation in the lipid profile in the endometrial thickness.
- No distressing side effects were noticed by any of the women except bloating in 9% women which was acceptable to them.
- In our study, we have not compared the results with placebo or HRT. Also, the symptoms were assessed subjectively. So possibility of bias cannot be ruled out. Therefore, further double blind long term trials are required before recommending phytoestrogens as first line therapy in symptomatic postmenopausal women.

### CONCLUSION

The present study entitled "Evaluation of Phytoestrogens as a Therapeutic Alternative to Hormone Replacement Therapy in Post-menopausal Women" was conducted in the Department of Obstetrics & Gynaecology of Rama Medical College Hospital & Research Centre, Mandhana, Kanpur, over a period of 12 months from August 2015 to July 2016 to evaluate the efficacy and side effects of Phytoestrogens.

- 90 cases were enrolled for the study with both natural and surgical menopause, out of which 75 cases could complete the follow-up schedule.
- Hot flushes were seen in maximum cases i.e. 88.6%, followed by lethargy in 76%, irritability 68.1% and sexual dysfunction in 60%.
- Phytoestrogens significantly reduced the incidence of vasomotor symptoms (19.3%), insomnia (4%), lethargy (11%), vaginal dryness (10%), hesitancy (1.7%), burning micturition (10.8%) and muscle, bone and joint pains (8%) after six months of regular therapy.<sup>(16,17,18,19)</sup>
- There was statistically significant drop in severity score at 6 months in vasomotor symptoms (1.0), insomnia (0.40), lethargy (0.29), vaginal dryness (0.48) and burning micturition (0.33).
- There was no significant variation in average body weight, blood pressure and lipid profile at the end of 6 months which implies the potential cardioprotective effect.<sup>(20,21,22)</sup>
- There was no significant variation in the endometrial thickness in 6 months which is a cancer protective sign. Therefore, to conclude, a good response was seen in most of therapy but prolonging the therapy for 6 months of reduced the severity score in most of the symptoms.
- In 6 month follow-up, no side effects were noticed except for mild bloating. Thus, phytoestrogenic preparations provide an attractive option for the management of postmenopausal symptoms and are free of side effects.<sup>(23,24)</sup>
- There is yet no definitive information in literature about the optimum dose and long term side effect. Therefore,

further long term double blinded multicentric trials are required before reaching to a definite conclusion. But in Indian scenario where postmenopausal women do not come for follow-up and investigations, phytoestrogens presently appear to be a safe and effective alternative.<sup>(25,26,27)</sup>

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