Clinical and Endocrinological Effects of a Menopausal Botanical Formula

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Abstract

Objective: To study the effects of a botanical formulation containing phytoestrogens on menopausal symptoms, serum gonadotropins and serum lipids.

Methods: 13 women with hot flashes, one other symptom of menopause, no menses for 3 months, a follicle-stimulating hormone (FSH) greater than 40 mg/ml, and no conventional hormone replacement therapy use within the last 3 months were admitted to the study. All women underwent a physical examination, complete with PAP smear. Data was collected through patient symptom diaries, physician symptom record and blood tests. A double-blind randomized controlled trial was utilized and six women received placebos and seven took 2 caps three times daily of verum.

Results: Seventy one percent (71%) of the women in the treatment group reported fewer total symptoms vs. seventeen (17%) in the placebo group. One hundred percent (100%) of the women in the treatment group experienced a reduction in their symptom severity vs. sixty seven percent (67%) in the placebo group. No significant changes occurred in serum gonadotropins or blood lipids.

Conclusion: Women with menopausal symptoms such as hot flashes, mood changes, insomnia, and vaginal dryness can experience improvement in the symptoms with the use of phytoestrogens while not raising serum estrogen and progesterone levels.

ORIGINAL RESEARCH

Introduction

A menopause supplement for the Journal of the American College of Obstetrics and Gynecology, OB-GYN states, "focus groups, involving women age forty to sixty, reveal that women know more about herbal medicines than about estrogen." (1) By the year 2015, nearly fifty percent (50%) of women in the United States will be menopausal. There are 20 million menopausal women currently in this country with the number expected to triple by the year 2010. Despite the orthodox physician's uniform advocacy for menopausal hormone replacement therapy (HRT) for all, only a fraction comply — fewer than twenty percent of women. Ninety percent of the women who begin HRT stop within the first year of use. Partially a failure of access and education, it is a testimonial to women's lack of trust in conventional medicine's safety, efficacy, and commitment to their well being.

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Currently, there are many unknowns about the relationship of HRT and breast cancer. Many women distrust and fear hormonal medicine and deny themselves potential benefit. An increasing number of women with high breast cancer risk are seeking alternatives to HRT.

Due to the need for symptom relief, many menopausal women seek out natural alternatives to HRT. Most of these therapies are utilized based on traditional uses of herbal medicines and years of empirical evidence on the part of alternative medicine. The purpose of this study was to begin the long road of discovering 1) which herbs can be used to reliably relieve different menopause symptoms, 2) determine whether or not the herbs raise serum estrogens and progesterone, decrease total cholesterol and/or increase high density lipoproteins (HDL), and 3) whether these herbs may be effective in managing osteoporosis and cardiovascular disease.

Materials and Methods

Over 125 women responded to a one line sentence in an article in *The Oregonian* (Portland,

OR) about menopause that stated the naturopathic college would be starting a research study on botanical alternatives to hormone replacement therapy. Sixty (60) women were screened out on the phone because they did not meet the basic criteria: hot flashes, one additional menopause symptom, no HRT for the previous 3 months, natural physiologic menopause with no menses for the last 3 months. Forty (40) women did not have a high follicular stimulating hormone (FSH) even though they met the symptomatic requirement. Thirteen women were ultimately enrolled in the study and 13 women completed the study. Other entrance criteria included no serious acute or chronic disease, no cardiovascular disease and normotensive.

Patients participated for a period of 3 months during which time the following steps were performed on each one:

1. Visit #1 = History, physical exam, and Pap smear
2. Return for blood draw for FSH
3. If greater than 40 mg/ml then the patient returned for blood tests: beta 17-estradiol, total serum estrogens, progesterone, cholesterol with HDL
4. Patients were blindly randomized into two groups, one picking up the placebo in the pharmacy, and the other beginning the botanical formula:

   Arctium lappa
   (Burdock root)
   2 parts

   Glycyrrhiza glabra
   (Licorice root)
   2 parts

   Leonorus cardiaca
   (Motherwort)
   1 part

   Angelica sinensis
   (Dong Quai root)
   2 parts

   Dioscorea barbasco
   (Mexican wild yam root)
   1 part

Capsules contained 500 mg of the combined dry herbs. Patients were instructed to take 2 capsules 3 times per day. Patients taking the placebo were instructed likewise. Placebo consisted of rice bran in similar (smell and appearance) cellulose capsules. (Dr. Hudson has acknowledged that the gamma oryzanol in the placebo, appreciated retroactively, may not be inert in terms of this study.)

5. Two week follow-up: Patients brought in their symptom diary. Physician also recorded each symptom. Both these charts were to be recorded on a scale of 0 to 3.
   0 = absent; 1 = mild;
   2 = moderate; 3 = severe
6. One month follow-up: Another session to note the patient symptom diary and allow for physician symptom recording.
7. Also at this one-month follow-up: Blood test repeated (FSH, beta 17-estradiol, total serum estrogens, progesterone, cholesterol, HDL).
8. Two month follow-up: Continued evaluation of patient quantitative symptom diary and physician symptom record.
9. Three month follow-up: Continued evaluation of patient symptom diary and physician symptom record.
10. At the 3 month visit, blood tests (FSH, beta 17-estradiol, total serum estrogens, progesterone, cholesterol, HDL) and the Pap smear were repeated.
11. Medications discontinued.

Rationale for the Botanical Formula

Arctium lappa (**Burdock root**). The active constituents are water insoluble, requiring methanolic extract. Of primary interest is a dismutagenic factor isolated from Arctium lappa. This factor reduced the mutagenicity of mutagens that are active without metabolic activation. (6) Also known to contain phytoestrogens. Traditional use in supporting liver metabolism of hormones.

Glycerrhiza glabra (**Licorice root**). The estrogenic activity of Glycyrrhiza glabra is due to the presence of beta-sitosterol, which is 1/400 as active as estradiol monobenzoate. (7) However, the glycoside of glycyrrehetinic acid has been shown to have an anti-estrogen activity; inhibiting the effect of estradiol on uterine growth in ovariectomized animals. (8) Additionally, glycyrrhiza polysaccharide increases the phagocytosis of macrophages (9) and a flavonoid was found to scavenge active oxygen free radicals. (10)

Leonorus cardiaca (**Motherwort**). The alkaloid leonurine is the active compound stimulating uterine activity. (11) Tradional use as a uterine tonic and general reproductive organ support.

Angelica sinensis (**Dong Quai root**) Antagonistic experiments suggest that the uterotonic activities of Angelica are due to a cholinergic component. (12) A combination of Peony, Angelica, Alisma and Cnidium increased progesterone secretion by effecting the corpus luteum. (13) Angelica is instrumental in stimulating corpus luteum progesterone even in the abscence of direct luteotropoic or luteolytic stimulation. (14) Additionally, depending on the dosage, sexual hyperfunction was observed when the extract (containing Angelica) was administered orally. Persistent administration exhibited a tendency toward inhibition of the estrus rate in mice. (15)

Dioscorea barbasco (**Mexican Wild Yam root**). Dioscorea has been used to treat coronary arteriosclerosis in China. (16) Wild Yam is popularly believed to be a phytoestrogen.

Results

Main clinical results are presented in Table 1. Women receiving verum (n=7) for 3 months showed a greater "response rate" than women in the placebo group (n=6). Response rate was calculated as the percent of patients in each group who showed a decrease in either the number or severity of symptoms from baseline to 3 months. Data summarized in Table 1 indicated that 100% of women taking the botanical formula had a reduction in their symptom severity scored form baseline to 3

Response Rate		
Symptom Severity	Placebo	67%
	Verum	100%
Number of Symptoms	Placebo	17%
	Verum	71%

Table 1

months, while only 67% of women receiving placebo showed a decrease. Seventy-one percent of women taking verum reported a reduction in the total number of symptoms, while only 17% of the women taking placebo reported a decrease in the total number of their symptoms. Since the hypothesis tested in this study was that the botanical formula would exert a positive result, a one-sided Z test was performed. This difference was statistically significant using a one-sided Z approximation to compare two independent proportions ($p<.03$). However, the use of a more stringent two-sided Z test did not reveal a significant difference.

Endocrinological results are shown in Figures 1-4. Serum follicle stimulating hormone (FSH) remained unchanged in both groups across the three months of the study (Figure 1). Nor were there clear effects of the botanical formula on either serum levels of beta 17-estradiol (Figure 2) or total serum estrogens (Figure 3). However, a trend was observed in the verum group indicating a decrease in serum levels of estradiol and total estrogens. A rise after 1 month in the placebo group was due to a single outlier patient. Serum progesterone levels also appeared to decrease in the verum group, and, by three months, average progesterone levels differed between placebo and verum groups, with verum showing a lower level than placebo.

Blood lipid results are shown in Figures 5-7. Serum cholesterol remained unchanged in the placebo group throughout. In the verum group, serum cholesterol dropped by 20 mg/dl at one month. Differences in changes in cholesterol from baseline to 3 months were compared between the two groups in a t-test for differences in means. Statistical significance was not attained ($p=.087$) despite the trend in the data seen in Figure 5. No clear effects of the botanical formula, distinct from placebo, were apparent in HDL cholesterol (Figure 6). Triglyceride results seen in Figure 7 show that the two groups differed in baseline levels and no clear conclusions can be drawn regarding the effect of the botanical formula on this blood lipid.

Discussion

The sample size of this controlled study does not warrant firm conclusions. Nevertheless, trends in the

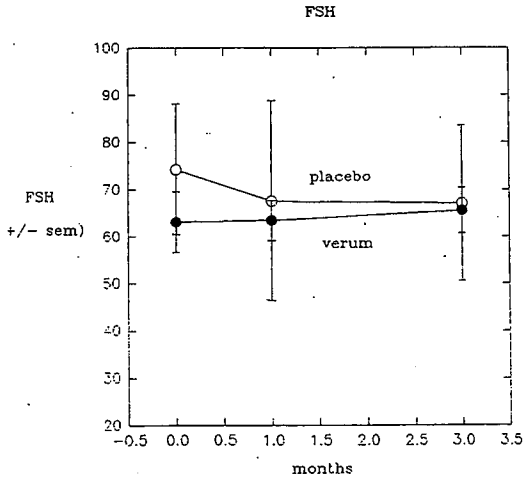

Figure 1

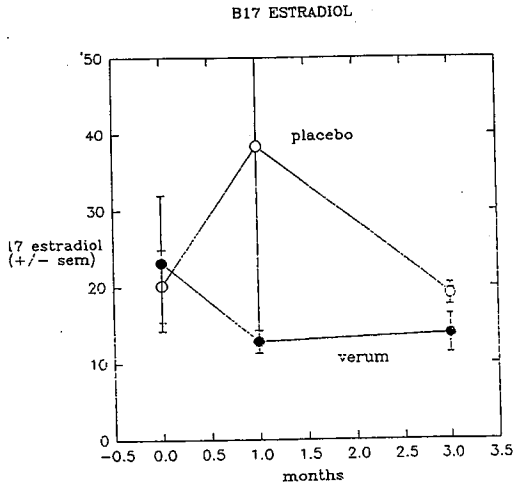

Figure 2

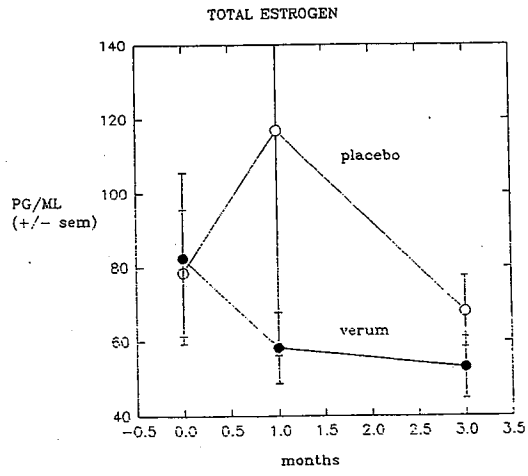

Figure 3

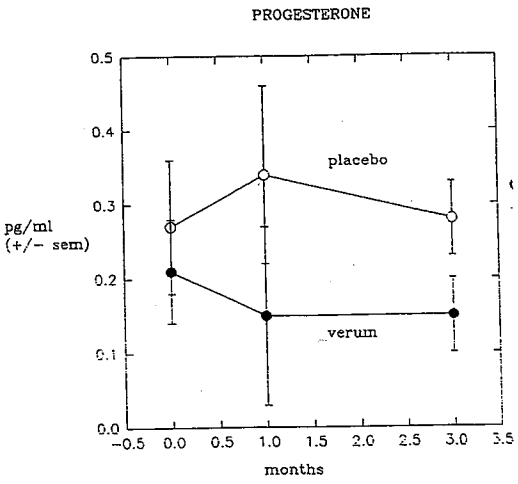

Figure 4

data suggest that despite changes in symptoms associated with the administration of a botanical formula, serum FSH does not decrease and serum estrogens do not increase. This small study, with only a total number of 13 participants, suggests that the formula's clinical effect does not depend on changing FSH or increasing estrogens and subsequent suppression of FSH at the pituitary gland. There have been previous studies to demonstrate that there may be as much as a 42% placebo effect on hot flashes. It is not surprising that patients of naturopathic physicians may experience an even greater placebo effect. This may be due to their hope and trust in alternative therapies or perhaps to the increased time that naturopathic physicians spend listening to their patients.

Although a drop in serum estrogens and beta 17-estradiol while using the botanical formula may not bode well for its value in preventing heart disease and osteoporosis, it may have strong implications for women who are breast cancer survivors or at high risk for breast cancer and become menopausal. Other studies on phytoestrogens such as soy and flax, with their high isoflavone and lignan content, respectively, demonstrate their possible value in postmenopausal breast cancer patients. They stimulate sex hormone binding globulin (SHBG) thereby resulting in decreased free estradiol levels. (2,3) They are competitive with estrogen for the binding sites thereby having an estrogen antagonistic effect. (4) They inhibit aromatase therefore reducing the conversion of androgens to estrogens. (4) Studies suggest that isoflavones may inactivate both the enzymes which create procarcinogens as well as inactivating carcinogens directly. (5) Studies with animal models using chemically induced mammary carcinogenesis demonstrated a protective effect of soy isoflavones by markedly reducing tumor formation. (5)

One could logically speculate that the phytoestrogens used in this formula may also have some of these effects. The trend towards reduction in estrogens in this study lends further credence to this possibility. Other possible mechanisms which could produce such a result could include the possibility that liver clearance of steroids is accelerated by the botanicals used in this formula. Perhaps estrogen producing tissues downregulate in the presence of phytoestrogens. It appears that the formula does decrease total cholesterol from above normal at baseline to almost 200 mg/dl by 3 months.

What is the mechanism of action of botanicals in relieving menopausal symptoms? Would this effect be lesser or greater in surgically induced menopause? Do phytoestrogens effect the adrenal glands, their production of androgens and consequently the overall total serum estrogens? Do botanicals containing phytoestrogens bind to estrogen receptor sites and compete with endogenous estrogens? Are phytoestrogens safe to use in women with uterine fibroids? Endometriosis? Endometrial hyperplasia?

This study raises more questions than it answers. However, the data suggest the following: This botanical formula can be effectively used to treat the symptoms of menopause especially hot flashes, mood changes, and insomnia. Given its minimal effect on FSH, serum estrogens, and progesterone, it can not be considered a reliable approach to addressing osteoporosis. In addition, bone mineral density studies need to be conducted on the use of phtyoestrogens in postmenopausal women. The effect of the botanical formula on cholesterol is encouraging for women who are hypercholesterolemic. Due to the potential of licorice root to elevate blood pressure, caution should be exercised against long term use and blood pressure should be monitored.

A future study is needed with a larger population

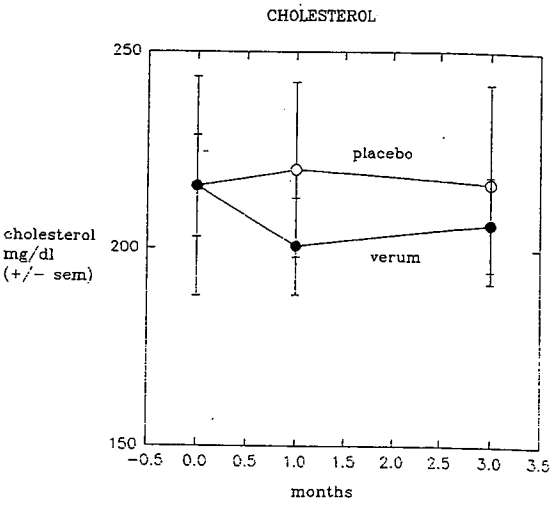

FIGURE 5

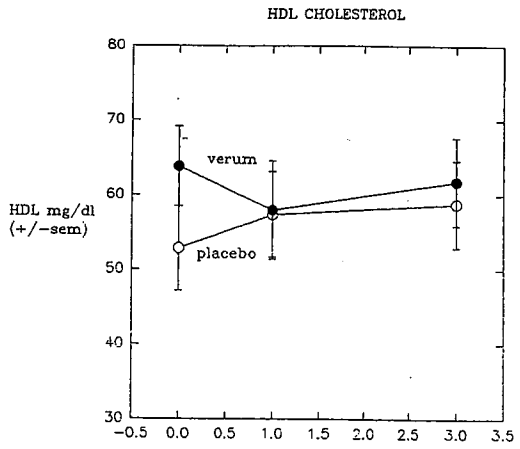

FIGURE 6

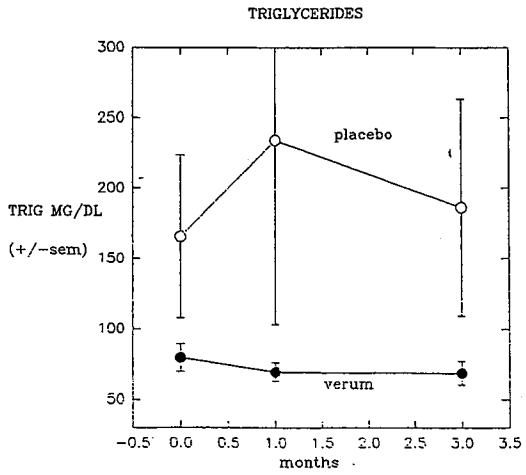

FIGURE 7

of women who are at least 12 months postmenopausal to clarify results and to assure stabilized gonadotropin levels. Other studies are needed to assess the role of medicinal plants in the prevention of osteoporosis and heart disease, as well as continued studies on symptom relief.

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