

Ultrasonographic Observation of the Breast in Early Postmenopausal Women during Therapy with *Cimicifuga Foetida* Extract and Sequential Therapy with Estrogen and Progestin

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Abstract

Background: It is now recognized that *Cimicifuga foetida* (*C. foetida*) extract is effective in alleviating menopausal symptoms. But the durations reported were usually short. The aim of this study was to investigate the effects of *C. foetida* extract therapy and different estrogen and progesterone sequential therapies, on the breasts of early postmenopausal women.

Methods: This was a prospective randomized trial. Ninety-six early menopausal women were recruited and randomly assigned into three groups treated with different therapies for 2 years. Patients were given *C. foetida* extract in Group A, estradiol valerate and medroxyprogesterone acetate in Group B, and estradiol valerate and progesterone in Group C. Ultrasonography was used to monitor changes in breast during treatment.

Results: In comparing breast glandular section thickness before and after 1 and 2 years of treatment, no significant difference was observed in Group A (11.97 ± 2.84 mm vs. 12.09 ± 2.58 mm and 12.61 ± 3.73 mm, $P > 0.05$); in Group B glandular section thickness had increased significantly (10.98 ± 2.34 mm vs. 11.84 ± 2.72 mm and 11.90 ± 3.33 mm, $P < 0.05$) after treatment, the same as Group C (11.56 ± 3.03 mm vs. 12.5 ± 3.57 mm and 12.22 ± 4.39 mm $P < 0.05$). In comparing breast duct width before and after 1 and 2 years of treatment, no significant difference was seen in Group A (1.07 ± 0.19 mm vs. 1.02 ± 0.18 mm and 0.98 ± 0.21 mm, $P > 0.05$); in Group B the duct width had a downward trend after treatment (0.99 ± 0.14 mm vs. 0.96 ± 0.22 mm and 0.90 ± 0.18 mm, $P < 0.05$), the same as Group C (1.07 ± 0.20 mm vs. 1.02 ± 0.17 mm and 0.91 ± 0.19 mm, $P < 0.05$). The nodules detected before treatment had disappeared after 1-year of treatment or exhibited no distinct changes in the three groups. However, new breast nodules had appeared after 2 years of treatment: There was one case in Group A, two cases in Group B and four cases in Group C, with breast hyperplasia after the molybdenum target check.

Conclusions: In early postmenopausal patients, *C. foetida* extract therapy and estrogen and progesterone therapy at low doses did not increase the incidence of malignant breast tumors.

Key words: Breast; *Cimicifuga Foetida* Extract; Hormone Replacement Therapy; Ultrasound

INTRODUCTION

The postmenopausal transition period and postmenopause are physiologic phenomena experienced by all women. They will suffer a series of physical and psychological symptoms, from the fluctuation in sex hormones or decrease in their levels before and after postmenopause. Hormone

replacement therapy (HRT) has been widely accepted as actively preventing osteoporosis after postmenopause, and relieving the syndromes associated with perimenopause and postmenopause. Thus, HRT can effectively improve the quality of life after menopause. However, the relationship between HRT and breast cancer is still in dispute, and has associated risks such as apoplexy and venous thrombosis,^[1,2] limiting its application in women with related risk factors. Nonhormonal drugs are well accepted owing to their limited

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side effects. *Cimicifuga foetida* (*C. foetida*) extract has been approved as a nonprescription drug for the treatment of early menopausal and perimenopause syndromes. In recent years, *C. foetida* has been used as a plant medicine in the domestic market; it is extracted from *C. foetida* and triterpenoid saponin is the main ingredient. Clinical trials have demonstrated that *C. foetida* extract was effective in alleviating the climacteric complaints of menopausal women.^[3,4] In the present study, ultrasonic technology was used to achieve the following: Monitor breast changes occurring during the clinical treatment of postmenopause related syndromes; evaluate the ultrasonic parameters before treatment, after 1-year of treatment and after 2 years of treatment in early postmenopausal women receiving *C. foetida* extract, estradiol valerate + medroxyprogesterone, and estradiol valerate + progesterone soft capsule therapy; and to evaluate the safety of the drugs regarding the breast as a reference for clinical medication.

METHODS

Participants

A total of 96 early postmenopausal patients were recruited from July 2009 to July 2010 at the Department of Gynecology of Peking Union Medical College Hospital, China. Participants were randomly and equally assigned into three groups by means of block randomization. The groups were: The *C. foetida* extract therapy group (Group A; 32 cases); the estradiol valerate and medroxyprogesterone acetate therapy group (Group B; 32 cases); and the estradiol valerate and progesterone soft capsule therapy group (Group C; 32 cases). The patients recruited were early menopausal, aged 40–60 years, and were experiencing climacteric symptoms. Patients in the early menopause stage were defined as going through amenorrhea for 6 months and within 5 years, as having a serum E2 concentration of <30 pg/ml, and a serum follicle-stimulating hormone concentration of >40 U/L. Major exclusion criteria included: The presence of uterine fibroids (fibroid diameter ≥ 5 cm or a uterus size equivalent to that measured at ≥ 8 gestational weeks); a history of diabetes or hypertension; a history of thromboembolism; severe endometriosis, epilepsy, asthma or hyperprolactinemia; a first degree relative having a history of breast cancer; undergoing HRT in the past 3 months; having experienced drug or alcohol abuse in the past 3 months; and an endometrial thickness ≥ 0.5 cm after withdrawal bleeding. Written informed consent was obtained from all of the patients before enrollment in the study. The study was approved by the Ethical Committee of the Peking Union Medical College Hospital.

Study design and treatment protocol

Patients were expected to take the medication over a period of 2 years. Patients in Group A took three tablets of *C. foetida* extract (100 mg/tablet) daily for 2 years. Patients in Group B took one tablet of estradiol valerate (E2V) for 30 days each cycle; from the 19th day, two tablets of medroxyprogesterone acetate (2 mg/tablet) were added to

the treatment and the therapy was continued for 24 cycles. Patients in Group C took one tablet of E2V for 30 days each cycle; from the 19th day they also took two capsules of progesterone (progesterone soft capsules) for 12 days, and the treatment was also continued for 24 cycles.

Ultrasonography system

All sonographic examinations were performed using a commercially available scanner (GE LOGIQ 5 PRO, Conn. Fairfield, CT in USA) equipped with an L5–L10 transducer for ultrasound. Machine presets for breast examination were selected so that multi-sectional scanning of the breasts could be conducted before treatment, and after 1 and 2 years of treatment. When undergoing scanning, the patients lay on their backs, with their two hands lifted high above the head and exposed their breasts; they were thoroughly scanned from the outer top to the outer bottom, from the inner top to the inner bottom in turn, making a straight cut, cross cut, and bevel cut. From the upper outer quadrant through to the cross section of the thickest part of the breast, we measured the largest anteroposterior diameter (i.e., the thickness of the breast glandular section through to the long axis section of the main duct below the papilla), and the internal diameter of the main duct. We recorded the thickness of the glandular section, the internal diameter of the duct, gland structure and color Doppler flow imaging. The average values for the thickness of the left and right breast and the internal diameter of the duct were obtained when collecting the data.

Indexes/variables

Patient data were recorded, including height, weight, body mass index (weight/height²), waistline, hipline, waist-hip ratio (waistline/hipline), blood pressure, pulse, and the results of regular physical and gynecological examination.

Statistical analysis

Data were analyzed using the SPSS software package version 13.0 (SPSS Inc., USA), and a $P < 0.05$ was considered as being statistically significant. Quantitative data were expressed as the mean \pm standard deviation (SD). In intra-group comparison between the data obtained before and after treatment, the paired-samples *t*-test was used if the data had a normal distribution; otherwise the Wilcoxon *W*-test was preferred. For comparison among the three groups, the one-way analysis of variances (ANOVA) was chosen if the data had a normal distribution and equal variance; when $P < 0.05$, least-significant difference was chosen for *post-hoc* multiple comparisons. An independent multi-sample rank sum test was employed when $P < 0.05$, and the Bonferroni method was used to conduct a two–two comparison.

RESULTS

General information

In comparing the general information for the three groups, there were no significant differences regarding age, height, body mass index and waist-hip ratio [$P > 0.05$; Table 1].

A total of 96 cases were recruited into the groups. Twelve cases withdrew after 1-year of treatment, including four cases in Group A, four cases in Group B and four cases in Group C. A total of 84 cases completed 1-year of treatment and evaluation. After 2 years of treatment, two cases had withdrawn in Group A and one case had withdrawn in Group C. A total of 81 cases completed the entire treatment and evaluation period of 2 years [Table 2]. The reasons for withdrawal mainly included the following: Unwillingness to take drugs because of headache; withdrawal owing to vaginal bleeding; reluctance to take drugs because of concern related to rash aggravation; refusal to take the drugs at all because of misgivings; refusal to take the drugs after undergoing surgery; and worries regarding hormone therapy. The real data were compared when collected.

Outcome measurements

Changes in the breast glandular section thickness before and after treatment in the three groups [Table 3]

In comparing the breast glandular section thickness after 1 and 2 years of treatment and before treatment, there were no significant differences in Group A ($P > 0.05$). In Group B, the breast glandular section thickness had an upward trend after 1 and 2 years of treatment, and there were significant differences (1-year, $P = 0.005$; 2 years, $P = 0.023$) as compared with the thickness before treatment. In Group C, the breast glandular section had a distinct tendency to increase in thickness after 1-year of treatment, and there was a significant difference ($P = 0.019$) as compared with the thickness before treatment. The breast gland thickness was reduced after the 2nd year of treatment, but its thickness was significantly greater than that before treatment ($P = 0.044$).

Comparison of breast duct width before and after treatment in the three groups [Table 4]

In Group A, breast duct width showed a gradual downward trend before treatment, and after 1 and 2 years of treatment, but there were no significant differences ($P > 0.05$). The change in breast duct width in Groups B and C had an identical gradual downward trend before treatment and after treatment, but there was no significant difference after 1-year of treatment ($P > 0.05$). The breast duct width had significantly decreased after 2 years of treatment relative to the width before treatment ($P < 0.05$).

Comparison of changes in breast structure before and after treatment in the three groups

In Group A, five benign breast nodules were detected using ultrasound before treatment; one nodule case had no obvious changes, and four cases had disappeared after 1–2 years of treatment. Seven new breast nodules were found after 1-year of treatment; one nodule case had no obvious changes, and six cases had disappeared after the 2nd year of treatment. One new nodule was found with a clear boundary after 2 years of treatment, without any blood flow by color Doppler, and the molybdenum target check result indicated mammary gland hyperplasia.

Table 1: Demographic characteristics of the patients in the three groups ($n = 32$ in each)

Characteristics	Group A	Group B	Group C	<i>P</i>
Age (years)	53.4 ± 2.9	52.1 ± 3.2	52.8 ± 3.5	0.293
Height (cm)	159.29 ± 4.82	159.46 ± 4.68	161.40 ± 3.70	0.129
BMI (kg/m ²)*	24.49 ± 0.46	23.05 ± 0.58	22.86 ± 0.56	0.074
W/H†	0.81 ± 0.04	0.82 ± 0.05	0.80 ± 0.05	0.145

*BMI: Body mass index; †W/H: Waist-hip ratio, waistline (cm)/hip circumference (cm).

Table 2: Time-related changes in the number of cases in the three treatment groups (n)

Groups	Before treatment	1-year after treatment	2 years after treatment
A	32	28	26
B	32	28	28
C	32	28	27
Total	96	84	81

Table 3: Thickness of breast glandular sections before and after treatment in the three groups (mm)

Groups	Before treatment	After treatment		<i>P</i>	
		1-year	2 years	1-year after versus before	2 years after versus before
A	11.97 ± 2.84	12.09 ± 2.58	12.61 ± 3.73	0.493	0.314
B	10.98 ± 2.34	11.84 ± 2.72	11.90 ± 3.33	0.005	0.023
C	11.56 ± 3.03	12.5 ± 3.57	12.22 ± 4.39	0.019	0.044

Table 4: Breast duct width of patients in the three groups before and after treatment (mm)

Groups	Before treatment	After treatment		<i>P</i>	
		1-year	2 years	1-year after versus before	2 years after versus before
A	1.07 ± 0.19	1.02 ± 0.18	0.98 ± 0.21	0.336	0.060
B	0.99 ± 0.14	0.96 ± 0.22	0.90 ± 0.18	0.534	0.024
C	1.07 ± 0.20	1.02 ± 0.17	0.91 ± 0.19	0.329	0.002

In Group B, eight benign breast nodules were detected ultrasound before treatment; one nodule case exhibited no obvious change, and seven cases had disappeared after 1 or 2 years of treatment. Two new breast nodules were found after 1-year of treatment; after the 2nd year of treatment, one nodule case showed no obvious change and in one case the nodule had increased in size, but there were no malignant signs and a further molybdenum target check indicated mammary gland hyperplasia. Two new nodules were found after 2 years of treatment. One nodule had a clear boundary without color signal, and

the nodule was considered benign and the molybdenum target check indicated breast hyperplasia. The other nodule had an irregular boundary, with disorder peripheral flow and arterial pulsed Doppler spectral waveform (the peak systolic velocity was 4.2 cm/s and the resistance index was 0.56) and the molybdenum target check indicated mammary gland hyperplasia.

In Group C, two benign breast nodules were detected using ultrasound before treatment. In one case, there was no obvious change in the nodule and in the other it had disappeared after 1–2 years of treatment. Two new breast nodules were found after 1-year of treatment. Four new nodules were found after 2 years of treatment with clear boundaries with no flow, and the molybdenum target check indicated mammary gland hyperplasia.

DISCUSSION

C. foetida has a medicinal history of nearly 200 years. Its rhizome extract is one of the available vegetable-based drugs. In North America and Europe, the isopropanol extract of black cohosh's rhizome (remifemin) is on sale as a nonprescription drug. It is listed as a vegetable drug for the treatment of dysmenorrhea associated with the climacteric syndrome and the premenstrual syndrome by German Commission E.^[5] Some researchers have demonstrated that black cohosh (one variety of cohosh grown in North America and Europe) can relieve postmenopausal syndromes.^[6-8] In the present study, the drug is an ethanol extract of the rhizome of *C. foetida* (usually called *Cimicifuga nanchuanensis* or west cohosh) containing 2 mg of 27-deoxidation *Cimicifuga* pavilion in each 33.3 mg extract. Its effectiveness in relieving postmenopausal symptoms has been proven in our previous study,^[9] but there are no published reports regarding its effectiveness in treating the breast in China. Our study used ultrasound to monitor the changes in breast structure, gland thickness and duct width to evaluate the effects of the *C. foetida* extract, and the changes in the breast after sequential treatment with various estrogen and progesterone regimens.

In the three therapy protocols used in the current study, the glandular section thickness had no trend regarding atrophy after 2 years of treatment. There was no significant difference in glandular thickness in the *C. foetida* extract treated group before and after treatment; thus, this extract was regarded as being effective in preventing the atrophy trend in breast thickness, but the detailed mechanism involved still requires further study. A significant difference was found in the glandular thickness in the other two hormone therapy groups after 2 years of treatment. This finding could be related to the influence of exogenous estrogen and progestin on the breast.

Some studies have reported that the breast duct gradually becomes wider after the menopause, probably related to the prolonged postmenopausal period, atrophy of the atini caused by a lack of estrogen and progesterone, flattening or

disappearance of the breast duct epithelial cells, and cystic dilatation of the lumen.^[10] In the current study, the breast duct had been prevented from expanding in width in the three groups. In Group A, the width of the breast duct had a downward trend after 1 and 2 years of treatment, but there was no significant difference ($P > 0.05$). The change in groups B and C had an identical downward trend, and there was a significant difference ($P < 0.05$).

The nodules detected before treatment and after 1-year of treatment disappeared or exhibited no distinct change in the three groups. New breast nodules had appeared after 2 years of treatment: There was one case in Group A, two cases in Group B and four cases in Group C, with breast hyperplasia after the molybdenum target check. Thus, it was found in the present study that *C. foetida* did not increase the incidence of malignant breast tumors after 2 years of treatment and estradiol valerate + medroxyprogesterone and estradiol valerate + progestin soft capsule therapy also did not increase the incidence of malignant breast tumors after 2 years of treatment.

Our study used ultrasound examination and the breast molybdenum target check to observe the changes in breast structure during treatment. Use of only one of these two check methods limits the accuracy of breast cancer identification while use of both methods increases the identification rate of this cancer. High-frequency ultrasound can clearly display skin, subcutaneous fat, glandular tissue, fascia and pectoral muscle. It can also detect small pathological changes in the breast and the surrounding tissues and small calcifications inside the breast; in addition, it can clearly reveal small structures in the various tissues of the breast without being influenced by the glands, and successfully observe the echo features and blood flow inside and around lesions.^[11,12] The main basis for assessing lesions using ultrasound is as follows: The grayscale ultrasonographic characteristics and colored blood flow distribution; the image features of pathological changes associated with anisotropic growth speed; infiltrative growth pattern; surrounding stromal reaction; and malnutritional calcification.^[13,14] The advantage of molybdenum target X-rays is its extreme sensitivity to the tumor nodule shadow and microcalcifications. The features of breast cancer are embodied in the easy identification of the molybdenum target, such as microcalcifications. Breast cancer readily occurs in middle-aged or elderly women whose breasts have partly degenerated and contain a considerable amount of fat, which facilitates a good comparison on the molybdenum target tablets. Although the molybdenum target shows a good image of the lesion outline, its disadvantage lies in its poor visualization of the internal structure of the lesion. The image is forward overlapped, and some of the lesions can be obscured by the glandular structure nearby, especially in women whose breasts are compact. However, these disadvantages can be compensated for using ultrasound examination; this can clearly show the tumor's location, shape, structure and its

invasion into the surrounding tissues. According to some studies, there is no significant difference in the accuracy rate of ultrasound and molybdenum target methods.^[15] Their sensitivity in detecting breast cancer is 80.2–90.7% for ultrasound and 82.7–83.3% for the molybdenum target method. Combination of the two imaging methods obviously increases the accuracy of breast cancer detection with an improved sensitivity of 93.8%.^[16-19]

The 2011 Guidelines of the International Postmenopause Association point out that hormone treatment has risks regarding breast cancer, thrombembolia, apoplexy and other conditions. *C. foetida* extract treatment is a good choice for the patients who worry about treatment risks. *C. foetida* extract is derived from the *Ranunculaceae cimicifuga* plant. In China, *Cimicifuga* was first recorded 2000 years ago in the text of Shennong's Herbal Classic as curing diseases.^[20] In the present study, after 2 years of treatment with *C. foetida* extract there was no significant difference in breast thickness, duct width and gland structure before and after treatment. Thus, no distinct effects regarding *C. foetida* extract were considered to have occurred in relation to the breast within 2 years of treatment.

C. foetida extract can be used to alleviate climacteric symptoms involving minor adverse effects, and is gaining popularity. As compared with hormone treatment, the different mechanism of action of this plant extract provides a new option for the treatment of patients with menopausal syndrome, who are not suitable or reluctant to accept hormone treatment.

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