

# A Pilot Observational Study to Assess the Safety and Efficacy of Menoprogen for the Management of Menopausal Symptoms in Chinese Women

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## Abstract

**Objective:** Over the past 5 years, the interest in alternative therapies for menopause has increased dramatically due to the findings of the Women's Health Initiative (U.S. National Institutes of Health). Menoprogen, a traditional Chinese medicine formulation is an herbal remedy that has been used in China for the management of menopause-related symptoms. An observational pilot study was performed to assess the effects of Menoprogen in the management of menopausal symptoms in perimenopausal and postmenopausal women.

**Design, subjects, and setting:** A multicenter prospective study was conducted at four clinical centers in China. Female subjects were eligible if they had menopausal diagnosis for at least 3 months and wished to use an alternative to hormone replacement therapy (HRT).

**Intervention:** Subjects received two capsules of Menoprogen (a combination product containing 0.2 g extracts of five herbs per capsule) orally, twice daily.

**Main outcome measures:** The primary outcome measured was an improvement of Kupperman Menopausal Index (KMI) from baseline. Secondary outcomes measured included hormone levels and the status of the endometrial and vaginal cytology after completion of treatment.

**Results:** After treatment with Menoprogen, a significant reduction in the KMI was observed (mean of paired difference = -14.875;  $p < 0.01$ ) as compared with baseline. Endogenous estrogen levels were significantly increased with Menoprogen (mean of paired difference = -3.145;  $p < 0.01$ ). Progesterone levels increased with Menoprogen (mean of paired difference = -10.003;  $p < 0.01$ ). Both follicle stimulating hormone (FSH) and luteinizing hormone (LH) levels showed significant before-and-after treatment difference (mean of paired difference = 6.125 mIU/mL for FSH and 4.938 mIU/mL for LH;  $p < 0.01$ ). No significant endometrial hyperplasia was observed post-treatment with Menoprogen. Most of the postmenopausal women exhibited a vaginal cell proliferation degree of 2–3, suggesting a possible estrogenic effect.

**Conclusions:** The present pilot study found that Menoprogen reduced symptoms associated with perimenopausal and postmenopausal complaints. Therefore, the rationale for a randomized, placebo-controlled clinical trial is supported.

## Introduction

The mid-life transitional period is regarded as a time of profound physical and psychological change for many

women.<sup>1</sup> The most obvious evidence of aging in middle-aged women is the climacteric associated with the decline in ovarian function that marks the transition to the end of the reproductive phase of life.<sup>2</sup> The climacteric begins several

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years before menopause, and it terminates when ovarian function ceases due to a decrease in circulating estrogen levels. Estrogen deficiency initially accounts for irregular menstruation and diminished vaginal lubrication. Continual estrogen loss is associated with changes in the vascular, muscular, and urogenital systems, as well as alterations in mood, sleep, and cognitive function.<sup>1</sup>

In the United States and Europe, many women use hormone-replacement therapy (HRT) to alleviate menopausal symptoms or to protect themselves against the chronic consequences of the menopause. However, since the publication of the Women's Health Initiative (WHI) of the U.S. National Institutes of Health,<sup>2</sup> concern about an increased risk of breast cancer, endometrial hyperplasia, and endometrial cancer associated with unopposed HRT has led women to actively seek alternatives to HRT.<sup>3</sup> In China, menopausal women have fewer symptoms, such as hot flashes and vaginal dryness, during the menopausal transition. These epidemiological findings have been attributed to the dietary habits of these populations, in particular the considerable use of traditional Chinese medicines rather than conventional HRT to relieve menopausal symptoms. Thus, prophylaxis and treatment of menopausal symptoms are relatively common indications for the use of Chinese traditional medicines in this population.

The product Menoprogen is an herbal combination based on an ancient Chinese medicine (TCM) formula. The product is composed of the extracts from five medicinal plants, namely *Lycium chinensis*, *Carthamus tinctorius*, *Laminaria japonica*, *Crataegus pinnatifida*, and *Morus alba*. Although this herbal formulation has been used in the management of menopausal symptoms in China for more than 10 years, there are few clinical data supporting its use. In one rodent study, histopathological assessment of rats treated with Menoprogen suggested that this TCM formulation may increase ovarian and follicular function by increasing endogenous estrogen.<sup>4</sup> Histopathological evaluation, as performed with electronic microscopy, indicated that apoptosis of ovarian granulocytes in aging rats was significantly reduced after treatment with Menoprogen.<sup>4</sup> A preliminary clinical study has also suggested that this traditional Chinese herbal combination was of benefit for the management of menopausal symptoms.<sup>5</sup> The aims of this pilot observational study were to obtain sufficient data on the efficacy and safety of Menoprogen in perimenopausal and postmenopausal women with menopausal symptoms, to warrant a randomized controlled clinical trial.

## Methods

### Formula and preparation of Menoprogen

Menoprogen is based on an ancient Chinese royal medicinal recipe. It contains highly concentrated aqueous extracts of five herbs: *Lycium chinensis* Mill. (Chinese wolfberry), *Carthamus tinctorius* (safflower), *Laminaria japonica* (sea kelp), *Crataegus pinnatifida* (hawthorne berry), and *Morus alba* (mulberry fruit). These herbal materials were locally cultivated and collected in China. Based on the physical and chemical characteristics of their unique active principles, the five raw materials were categorized into two groups to isolate polysaccharide and flavone constituents by bioassay-guided extraction and semi-purification techniques specific for those

active principles fractions from the five raw plant materials. These processes enable preservation of the active components in the same proportions in which they occur in the raw herbal materials. In the final formulation, the polysaccharides and flavones were measured at  $\geq 30\%$  and  $\geq 20\%$  of total ingredients, respectively. After making the appropriate composition ratio of the active concentrated individual extracts in the final formula, Menoprogen was encapsulated. The product Menoprogen is a proprietary compound for which a patent is currently pending.

### Subjects

This study was a usual-care, multicenter prospective trial of 83 women 40–65 years of age with menopausal symptoms. The subjects were perimenopausal and postmenopausal outpatients for whom the physicians had prescribed either HRT or natural herbal alternatives as part of their normal standard of care.

Subjects were eligible for this study if they had a medical diagnosis of menopausal symptoms for  $\geq 3$  or more months based on the guideline for use of botanicals for management of menopausal symptoms.<sup>6</sup> Subjects were entered into the study if they had not been previously treated for menopausal symptoms or if they had a relapse of menopausal symptoms and had not been treated with HRT or alternative therapies within the 3 months prior to the study. Subjects with a modified Kupperman Index (KMI) score  $\geq 15$  were included in the study.<sup>7</sup>

Subjects were excluded if they had a co-morbid malignant illness, a history of complete ovariectomy, any illness or disturbance that could preclude participation in the trial, any contraindication to use of any of the components of Menoprogen. Concomitant treatments or medications prescribed for the relief of menopausal symptoms or conditions were not allowed, other than as specified in the exclusion criteria. The study protocols were approved by all of the participating Centers, and a written informed consent for study participation was obtained from all subjects. The primary outcomes for this study were measured in subjects who were maintained on Menoprogen capsules for at least 3 months, and had at least two measurements on the modified KMI<sup>7</sup>; the secondary outcomes assessed included levels of plasma estradiol and progesterone, endometrial thickness, and vaginal cytology at baseline and/or during the course of the study.

### Interventions

Of the 107 women initially screened at the four sites, 83 met the eligibility criteria and received two oral doses (two capsules per dose) of Menoprogen daily for at least 3 months. Each capsule contained 0.2 g of the herbal extract combination (equivalent to 110 g of crude herbal materials). For the sake of compliance, subjects were encouraged to use Menoprogen consistently for relief of menopausal symptoms. Subject study eligibility was performed by a trial nurse who administered a predefined self-evaluation questionnaire completed by each of the study participants.

### Outcome measures

The KMI has been used in many similar studies, and although it is not perfect, it is generally regarded as a valid,

reliable, and responsive efficacy criterion.<sup>7</sup> The treatment outcomes in the modified KMI were used to measure the impact of treatment on menopausal symptoms over time. In this study, the focus was on the menopause-specific segments of the weightings suggested by Kupperman, which rates menopausal symptoms on a visual analogue scale divided into four sections: hot flushes, psychologic, vasomotor, and urologic).<sup>7</sup> The modified KMI includes 12 symptoms that weigh hot flushes by a factor of four, psychologic symptoms by a factor of two, and vasomotor and urologic symptoms by a factor of one.<sup>8</sup> Each symptom was scored on a four-point severity scale from 0 = none to 3 = severe. These severities were then summed across the 12 symptoms as index = factor × scale. Useful categories for describing clinical relevance of the index were: > 35 (severe), 20–35 (moderate), 15–19 (light moderate) and < 15 (mild).

*Hormone, LH, FSH, analysis*

Blood samples obtained at screen/baseline were analyzed by radioimmunoassay for estradiol, progesterone, luteinizing hormone (LH), and follicle-stimulating hormone (FSH) to assure the diagnosis of premature ovarian failure due to menopause. Blood samples obtained at the end of 3 months of treatment were analyzed for estradiol, progesterone, LH, and FSH to assess ovarian function. For perimenopausal women, the hormone assessment was performed on blood samples collected on the third day after the normal menstrual period. The blood samples were frozen at -70°C until the collection of all samples pre- and post-Menoprogen was completed. All blood samples were then assayed by a radioimmunoassay.

*Ultrasonography and vaginal cytology*

Ultrasonographies were performed by a single operator using a Power Version 1000 ultrasonographer fitted with a 5.5 MHz transvaginal probe (Aroka, Japan). The endometrium was measured by longitudinal scans at the point of maximum thickness, including both endometrial outer limits, assuming that the amount of intracavitary fluid was not significant. In all cases, a mean of three measurements was considered at baseline, at the end of 3 months, and at 3-month intervals up to 12 months. Evaluation of physiologi-

cal effects of Menoprogen was based on vaginal cytology measures together with the hormone levels as described above. The vaginal cytology parameter measured was the degree of cell proliferation in the vaginal epithelium (according to Schmitt's graduation scale), according to the eosinophilic index (the ratio of eosinophilic/basophilic surface cells found in the smear) measured using the smear technique and Bashi dying at baseline and at the end of 3 months to determine the impact of treatment on the vaginal epithelium.<sup>9</sup> Safety was assessed by the incidence self-reported adverse events, and by routine hematological and biochemical tests.

*Statistical analysis*

The data presented are based on evaluable analysis. All measurements were listed and/or tabulated, and means and standard deviations, where appropriate, were calculated. Changes in the modified KMI from baseline to the end of 3 months or the final study visit were evaluated. Continuous variables were analyzed using the paired *t*-test. A value of *p* < 0.05 was regarded as statistically significant.

**Results**

*Samples*

Four centers and seven gynecologists participated in the pilot observational study in both the United States and China. In total, 107 menopausal women were recruited (Fig. 1), 83 of whom completed baseline and follow-up Kupperman Index; the other 24 women were classified as non-completers (10 were ineligible and 14 were lost follow-up). Of the 83 participants, 73 completed the modified KMI and assessment of hormonal levels at the end of 3 months, and the other 10 women completed the modified KMI only. Of those who completed the KMI scoring, 36 postmenopausal women treated with Menoprogen for more than 6 months were evaluated for vaginal cytology parameters, and endometrial thickness measurements were obtained for 59/73 menopausal women. Of these 59, 27 were followed for an additional 9 months, 18 for 12 months, and 14 for more than 1 year.

Table 1 displays the demographic and clinical characteristics of the evaluable subjects, all of whom were Chinese women whose average age was 50.

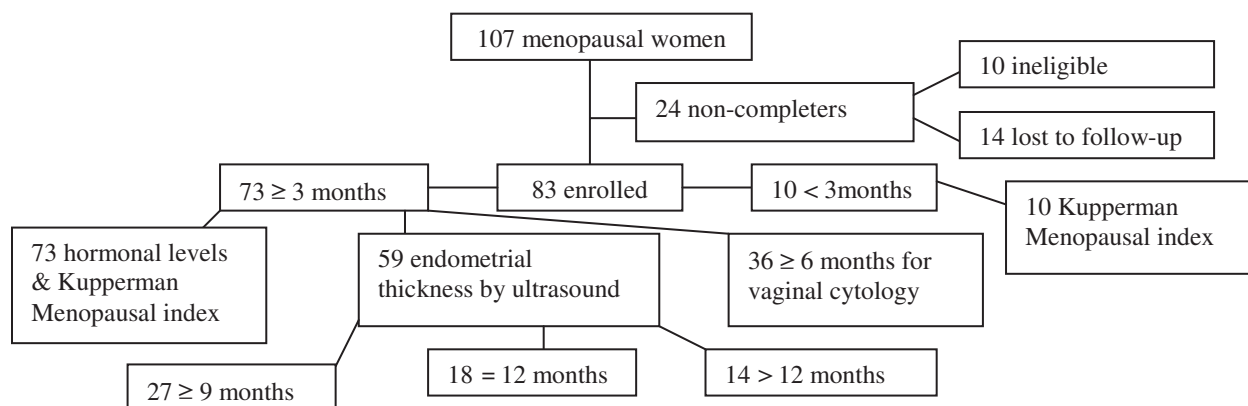


FIG. 1. Subject disposition.

TABLE 1. DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF ITT STUDY PARTICIPANTS

Characteristics	ITT evaluable (n = 83)
Age (years)	
40–44	3
45–49	38
50–54	36
55–60	4
>60	2
Height (cm)	158
Body weight (kg)	56
FSH (mIU/mL) <sup>a</sup>	79.9 ± 17.3
LH (mIU/mL) <sup>a</sup>	33.1 ± 9.2
Employment status	
Full-time workers	47
Part-time workers	15
Retired	18
Other	3
Physical exercise (walking)	
Low (<1 hour/day)	23
Moderate (>1 hour/day)	36
Intense (>1 hour/day)	24
Years since menopause	0.5–8

<sup>a</sup>Values are means ± standard deviation.

ITT, intended to treat; FSH, follicle-stimulating hormone; LH, luteinizing hormone.

### Efficacy parameters

A significant reduction in the modified KMI score was observed after treatment of with Menoprogen, indicating a reduction in menopausal symptoms (Table 2). The mean reduction from baseline of the modified KMI score was significant ( $-14.875$ ;  $p < 0.01$ ) after 3 months of treatment with Menoprogen.

Figure 2 shows the improvement in individual menopausal symptoms reflected by the change in Kupperman Index score before and after treatment with Menoprogen. The lower KMI score and the improvement in menopausal symptoms after treatment with Menoprogen paralleled the changes in the plasma hormone levels (Table 3). Compared with mean estrogen (E2) and progesterone (P) levels measured prior to administration of Menoprogen, the E2 and P levels increased significantly in menopausal women treated with Menoprogen ( $p < 0.05$ ), and the E2 level increased to an mean of paired difference of  $-33.145$  pg/ml ( $p < 0.001$ )

and  $p$  level mean of paired difference of  $-10.003$  pg/ml ( $p < 0.01$ ). Both FSH and LH levels showed significant before-and-after treatment means of paired difference of 6.125 and 4.938 mIU/mL (all  $p < 0.05$ ), respectively.

The endometrium is an exceptionally sensitive indicator of estrogenic effects.<sup>8</sup> Women who continue to take unopposed estrogen therapy typically have endometrial hyperplasia.<sup>10</sup> In this study, no statistical difference in endometrial thickness was observed post-treatment, even in women taking Menoprogen for 12 months or more. The vaginal exfoliative cytological examination assessed the degree of change in cell proliferation in menopausal women treated with Menoprogen. After 6 months, most postmenopausal women reached a cell proliferation degree 2–3 (mostly intermediate and scattered surface cells). Two postmenopausal women had a proliferation cell status of degree 3–4, indicating dominance of outer surface cells. Similarly, the eosinophilic index was designed to assess the cellular proliferation status (Table 4). After taking Menoprogen for 6 months, most of the women showed an index value greater than 20% of normal, and in five cases the value was over 50%, i.e., the surface cells became dominant. The 36 postmenopausal women had an average index value of 18%–35% after the therapy, which was coincident with an increase in vaginal secretions reported in the self-evaluations recorded by these women.

### Adverse events

The data from routine blood samples showed no significant adverse difference before and after treatment with Menoprogen. Women who continuously take estrogen products usually experience abnormal menstrual periods or intermittent spotting. In the present study, no such abnormalities were observed in women treated with Menoprogen. The only adverse event reported in the study was mild stomach upset in 2% of subjects. After the subjects were advised to take Menoprogen after meals, this adverse event was prevented.

### Discussion

In Asia, women reach menopause at a median age of 51 years<sup>11,12</sup> similar to women in the United States.<sup>13</sup> The vasomotor symptoms of Asian women are somewhat less severe than women in the U.S., but Asian women tend to have more vasomotor symptoms during the perimenopausal transition.<sup>11,12,14</sup> Psychological symptoms (depression, irritability, nervousness) are similar to those observed in U.S. women; poor education and low socioeconomic status are associated with a higher symptom rate in all populations.<sup>13</sup>

TABLE 2. THE PAIRED TEST FOR THE INDEX OF KUPPERMAN SCORE BEFORE AND AFTER TREATMENT (SUBJECTS)

		Paired differences			5% Confidence interval of the difference		T	Sig. (2-tailed)
		Mean	SD	SEM	Lower	Upper		
Pair 1	Z_b-Z_A	14.875	10.566	1.671	11.496	18.254	8.903	0.000

Z\_b, pre-treatment; Z\_A, post treatment; SD, standard deviation; SEM, standard error of the mean.

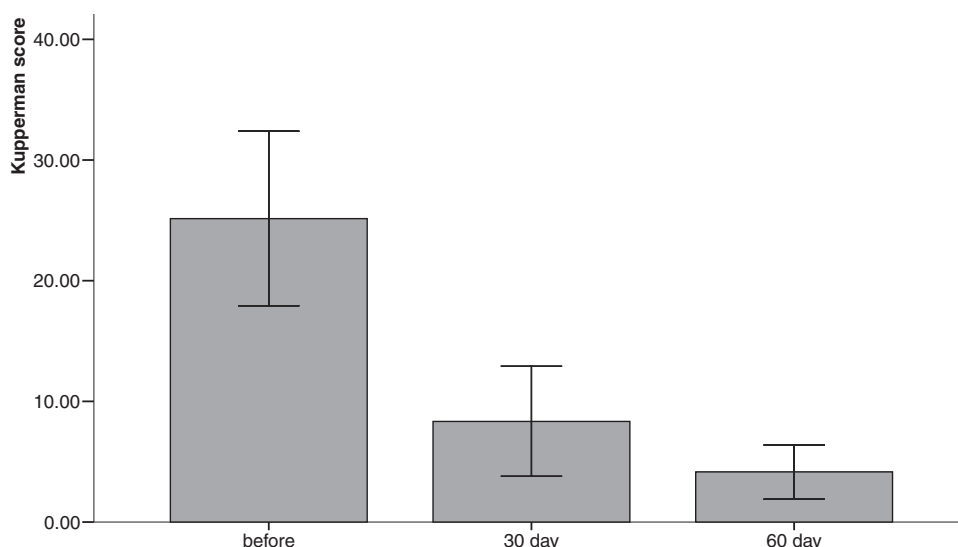


FIG. 2. Comparison of treatment effectiveness with Menoprogen 30 days and 60 days post-treatment to pretreatment, respectively.

The results of one study show that 20.3% of Taiwanese women used TCM for relief of menopausal symptoms, and that 54% of them found significant to moderate relief of symptoms.<sup>15</sup> This indicates that TCM have strong potential for development into treatment for menopause.

The traditional Chinese herbal medicine, Menoprogen, was developed based on the ancient royal medical formula and theory of traditional Chinese medical practice.<sup>16</sup> Traditionally, the combinations of these herbs were used to manage menopausal symptoms. In the theory of Chinese traditional medicine, reproductive function is related with renal function, and the dysfunctions related to menopausal symptoms are assumed to reflect a deficiency in kidney-Yin. Varieties of herbal compounds are designed to harmonize the deficiency of kidney-Yin. Some studies have demonstrated that the menopause-treatment compounds play biological roles by managing the neuro-endocrine-immuno network (NEI-N) system or by invigorating failing ovarian functions, such as removal of free radicals, improvement of microcirculation, and postponement of cellular apoptosis.<sup>17</sup> It has been found that the follicle atresia in the ovary resulted from

natural apoptosis of granulosa cells related to reductions of hormonal reduction, or disorder of cellular factors and genomic expressions.<sup>18</sup>

Obviously, the improvement of hormonal levels as well as bringing the hypothalamopituitary gland-sexual gland system into harmony might benefit from postponement of the ovarian senile dysfunctions. It is believed that the herbal compounds may balance the kidney-Yin by managing the process of folliculogenesis and improving immune functions in women in menopause,<sup>19</sup> a result far superior to the effects of conventional HRT.

The semi-purified extracts from Chinese wolfberry, hawthorn berry, and mulberry fruit, which are major herbal components in Menoprogen, and which have been employed to treat hot flushes and are known for increasing production and circulation of blood to the ovarian and uterine tissues within organ-specific microenvironment. Thus, according to traditional Chinese medical theory, the ovarian and uterine tissues are fully nourished and in harmony. In earlier pharmacological studies on aged female rats, Menoprogen was found to have pleiotropic effects on the endocrine system,

TABLE 3. THE PAIRED TEST FOR FEMALE HORMONAL LEVELS AND DISPOSITION AFTER TREATMENT

		Paired differences			5% Confidence interval of the difference		T	Sig. (2-tailed)
		Mean	SD	SEM	Lower	Upper		
Pair 1	FSH-FSH_A*	6.125	6.243	0.987	4.126	8.121	6.205	0.000
Pair 2	LH-LH_A	4.938	4.863	0.769	3.382	6.493	6.422	0.000
Pair 3	E2-E2_A	-33.145	61.396	9.960	-53.325	-12.965	-3.328	0.002
Pair 4	P-P_A	-10.003	12.993	2.054	-14.158	-5.848	-4.869	0.000

\*FSH, LH, E2, and P = pre-treatment; FSH\_A, LH\_A, E2\_A and P\_A = post-treatment. SD, standard deviation; SEM, standard error of the mean; FSH, follicle-stimulating hormone; LH, luteinizing hormone.

TABLE 4. EOSINOPHILIC INDEX DISTRIBUTION AFTER TREATMENT IN MENOPAUSAL WOMEN

Eosinophilic index (%)		<10	11–20	21–50	>50	Mean
Menopausal women	Pre-therapy	15	18	3		18%
	Post-therapy	3	4	24	5	35%

resulting in enhanced function of aging ovarian tissues, as well as rejuvenation of the pituitary-ovarian-uterine system.<sup>4</sup>

In this pilot, observational study, the results indicate that treatment with Menoprogen for at least 3 months can significantly reduce menopausal symptoms, as assessed by the modified KMI. Increases in the blood concentration of estradiol and progesterone were also noted, and they remained stable even after use of the product was discontinued. The increased estrogen and progesterone levels were correlated with the quantities of intermediate or surface cells found in the evaluation of vaginal exfoliative cells. Our data from the vaginal cytology support the previous evidence that Menoprogen may restore moderate estrogenic activities of ovarian tissues by re-energizing ovarian function.<sup>4</sup>

We also found that a high proportion of subjects who took Menoprogen in the study experienced a reduction in FSH levels for the mean of paired difference of 6.125 mIU/mL. That value was much lower than the FSH levels commonly observed in menopausal women.<sup>20</sup> This decrease in FSH concentrations may be due to negative feedback through increasing endogenous estrogen concentrations. In other words, the generation of endogenous estrogen by Menoprogen may result from other mechanisms than the elevation of FSH concentration. Macklon and Fauser<sup>18</sup> have indicated that other growth factors can affect estrogen production, such as inhibin, epidermal growth factor, and insulin-like growth factor binding protein (IGFBP), and have an inhibitory effect on the response of cultured granulosa cells to FSH. To clarify this apparent paradox, it is necessary to have further investigations into the molecular pharmacological mechanism of Menoprogen.

The results of the present observational study confirmed that, although menopausal women took Menoprogen for up to 12 months, there was no significant endometrial hyperplasia; nor was there irregular vaginal bleeding or spotting, although some of the postmenopausal women began to menstruate. Warren et al.<sup>10</sup> have concluded that women receiving external hormonal therapy are generally amenorrhoeic after a period of irregular bleeding at the beginning of the therapy, and they show an atrophic endometrium. Therefore, it does not appear that Menoprogen acts as a phytoestrogen, but instead enhances the levels of endogenous estrogens. It may also work by modulating the pituitary-ovary system and its relevant tissues/organs, as demonstrated in earlier animal studies.<sup>4</sup> Thus, Menoprogen may have pleiotropic effects that work together to reduce menopausal symptoms.

To determine if Menoprogen was acting as a direct phytoestrogen itself, this study looked at the proliferation of the vaginal epithelium, an exceptionally sensitive indicator of an estrogenic effect. The degree of cell proliferation and the eosinophilic index were both monitored. Only intermediary cells or intermediary cells with individual outer surface cells

were observed in the vaginal smears (proliferation degree 2–3 or 3–4). Based on the vaginal cytology data from this study, together with hormone levels (FSH, LH, E2) measured during the study (i.e., LH and FSH levels both decrease because of the E2-induced negative feedback mechanism), it is possible that Menoprogen indirectly induces an estrogen-like effect on ovarian tissues. Our data suggest that Menoprogen treatment is associated with an increase in endogenous estradiol and progesterone, suggesting a possible follicle-development rejuvenation mechanism without FSH involvement.

This observational trial included some menopausal women who had a previous history of HRT. We found that those women who had received HRT for more than 6 months responded slowly to Menoprogen and responded poorly as compared with those women who had not been treated with HRT. Women previously treated with HRT took as long as 2–3 months after the administration of Menoprogen to respond, whereas the menopausal symptoms of women who had never received HRT were improved as soon as 2 weeks after beginning treatment with Menoprogen. Also, older postmenopausal women (age  $\geq 65$ ) did not observe any reduction in symptoms until 3–5 months into treatment. Women 50 years of age or younger generally showed significant improvement within 2 months after beginning treatment with Menoprogen.

The clinical response to Menoprogen seemed to be related to the existence of intact ovarian tissues. Our previous experience had indicated that for menopausal women who had a full ovariectomy, treatment with Menoprogen did not reduce hot flashes. However, for those women who had a partial ovariectomy, the effects of Menoprogen took longer to observe. These data suggest that the magnitude of Menoprogen effect is dependent on ovarian function. Once the ovarian tissue function declines with age, and is atrophied by HRT or damaged by ovariectomy, ovarian function cannot be reinvigorated.

Admittedly, there are numerous limitations to the present study, including the fact that it was neither randomized nor blinded. Nonetheless, the results are striking and unlikely to have resulted from biases because similar findings were observed in all study centers. The significant reductions in the KMI scores along with the total lack of toxicity indicate that further randomized controlled clinical trials assessing safety and efficacy of Menoprogen are warranted.

## Conclusions

The results of this pilot study show that the effects of Menoprogen were cumulative and that this product maybe useful for prolonged therapy. Many of the women who received Menoprogen observed an initial effect within 1–2 weeks after beginning treatment and attained the optimal ef-

fects 2–3 months into the treatment. Women who were treated with Menoprogen for one year or more experienced sustained effects for 1–2 months after they stopped treatment. These data suggest that symptomatic perimenopausal women just entering the menopause transition may be the most appropriate population for treatment with Menoprogen. More important no serious adverse events were reported throughout this study of women from this age group.

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