**Therapeutic Effect of *Vitex Agnus Castus* in Patients with Premenstrual Syndrome**

Mehrangiz Zamani, Nosrat Neghab, and Saadat Torabian

1 Department of Obstetrics & Gynecology, Hamedan University of Medical Sciences, Hamedan, Iran
2 Department of Community Medicine, Hamedan University of Medical Sciences, Hamedan, Iran

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**Abstract**

Medical therapies have been widely used for premenstrual syndrome (PMS), but in all of them side effects are predominant. Herbal remedies rarely have side effects and people have more tendencies toward them than chemical therapies. In this study the therapeutic effect of *Vitex agnus castus* on women who had the PMS, in comparison with placebo, were investigated. In this randomized, placebo-controlled, double-blind study, from 134 selected patients 128 women suffered from PMS were evaluated (active 62, placebo 66). All patients answered to a self-assessment questionnaire about their headache, anger, irritability, depression, breast fullness and bloating and tympani during the premenstrual period before the study. Forty drops of Vitex agnus extract or matching placebo, administrated for 6 days before menses for 6 consecutive cycles. Patients answered the self-assessment questionnaires after 6 menstrual cycles, again. Each item rated using a visual analogue scale (VAS). The mean age was 30.77 (SD=4.37) years in the active group and 30.89 (SD=4.02) years in the placebo group. Rank of variables had significantly difference in active and placebo group before and after the study (P<0.0001) also we noticed significant differences on the use of *Vitex agnus* in comparison with placebo (P<0.0001). *Vitex agnus* can be considered as an effective and well tolerated treatment for the relief of symptoms of mild and moderate PMS.

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**Keyword:** *Vitex agnus castus*; Premenstrual syndrome; Botanical supplements

**Introduction**

Premenstrual syndrome (PMS) is a complex combination of psychological symptoms and somatic changes that occurs in 1-2 weeks before menstruation period of women (1-5). Several medical therapies and herbal remedies have been reported to relieve PMS symptoms (6-8).

Nearly 50% of women in fertility ages experience PMS. Physical, psychological and behavioral disturbing changes of PMS are intensive enough to cause disturbance in the interpersonal relations and normal activities (3,4,6,9). The PMS is defined as symptoms have occurred during the last week of the luteal phase (premenstrual phase) in most menstrual cycles for the past year. Within a few days of the onset of the follicular phase (menses), the symptoms begin to remit and are absent in the week following menses. Five or more of the following symptoms have to be present for most of the time during the last week of the luteal phase, with at least 1 of the first 4 symptoms: 1) depressed mood; 2) tension or anxiety; 3) affective liability or tearfulness; 4) irritability or anger; 5) decreased interest in usual activities; 6) difficulty concentrating; 7) fatigue or lethargic; 8) changes in appetite; 9) hypersomnia or insomnia; 10) feeling overwhelmed; and 11) Physical symptoms (breast tenderness, headaches, bloating, muscle pain). These symptoms are not merely an exacerbation of the symptoms of another disorder, such as major depressive disorder, panic disorder, dysthymic disorder or a personality disorder, but may be superimposed on another disorder. The presence of the symptoms must be confirmed by prospective daily ratings during ≥2 consecutive symptomatic cycles (10).

In addition to training, consultation, diet changes, medical interventions and supplements, there are various botanicals which are useful in the treatment of PMS. In spite of a broad spectrum of the effective drugs for PMS, the attempts still continue to find a drug with the most efficiency and the fewest side effects. In this study we...
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used chastet berry. Its botanical name is *Vitex agnus castus berries*. Chaste berry is derived from the Greek word Chastity, which means chaste, because it was used to reduce sexual intentions in ancient Greece and Rome (11-14). The fruits of *Vitex agnus* contain a mixture of iridoids and flavonoids, and some compounds similar in structure to the sex hormones have been isolated from the leaves and flowers. The mechanism of action may also be related to modulation of stress induced prolactin secretion via dopamine, without directly affecting LH and FSH. Binding to opioid receptors, endorphins, and neuroactive flavonoids may also have a role (6).

Some side effects of *Vitex agnus* are minor dermal problems and some intestinal problems such as diarrhea, headache, vertigo and palpitation, which disappear after stopping its use (15,16). There are no reports of herb-drug interactions involving *Vitexagnus*. Some herbalists believe that *Vitexagncould interfere with birth control pills, hormone replacement therapy, and other hormone replacement medication* (16). Additionally, it has been hypothesized that individuals taking drugs classified as dopamine-receptor antagonists should use caution when taking *Vitex agnus* because animal studies indicate that *Vitex agnus may interfere with the dopamine receptors* (9,17).

Several studies have been done to check the *Vitex agnus* effects on PMS and most of them have revealed its significant effects on decreasing or improving PMS symptoms (18-20).

Since PMS is one of the restrictive causes in daily women’s activities and its excitation has some effects on several aspects of personal life, accessing and studying a method with a few side effects and an easy on several aspects of personal life, accessing and studying a method with a few side effects and an easy procedure can satisfy fertility program purposes (1,2,6).

In most of the studies, patients received 20-40 drops of *Vitex agnus* extract (3.5-4.5 mg) 3 times a day for 3-6 months. Then its effect on PMS determined (7,18-20).

Due to its bitterness and therefore poor compliance in daily usage, we implemented a new method for the drug consumption.

Materials and Methods

In this randomized, placebo-controlled, double-blind, cross-over study, all the child bearing age patients who had referred to Fatemie Hospital Clinic (University hospital, Hamedan, Iran) from December 2006 to January 2007 were evaluated by DSM-IV criteria regarding PMS. A detailed history of pregnancy, weaning, contraception, mental diseases and drugs consumed for major depression (which imitates PMS signs) and other diseases were obtained. Inclusion criteria were reproductive age women, regular menstrual cycles lasting 25-34 days, and met DSM-IV criteria for PMS. Exclusion criteria were pregnancy and breast feeding, inadequate contraception, drug and alcohol abusers, patients with pituitary problems, those who had used sexual hormones other than oral contraceptive pills (for which the doses were kept unchanged) and previous *Vitex agnus* users concomitant psychotherapy, concomitant serious medical condition, hypersensitivity to *Vitex agnus*. PMS diagnosis is futuristic therefore PMS criteria were based on Penn daily symptom reports (DSR) rated by the subjects for two menstrual cycles prior to commencing study. The aim of this screening period for two menstrual cycles was to screen the patients for suitability and to confirm the diagnosis of PMS. Each item was rated by on a five-point scale daily (0=none to 4=extreme). Scores were calculated by summing the ratings of cycle days 5-10 for postmenstrual score (day 1 was the first day of the menses) and the ratings of cycle days 23-28 for the premenstrual score. DSR criteria for this 2 month open-label screening were an increase of 30% or over in total premenstrual DSR scores (days 23-28) compared with the postmenstrual scores (days 5-10) (22).146 women were screened and 128 patients were evaluated. The patients were randomly divided by a computer-generated schedule into control and experiment groups.

Sample size was calculated by this formula:

\[
n = \frac{1}{1 - F} \left( \frac{z_\alpha + z_\beta}{P - q_0} \right)^2 = 73
\]

\[
\alpha = 0.05 \rightarrow z_\alpha = 1.96
\]

\[
\beta = 0.2 \rightarrow z_\beta = 1.28
\]

\[
P = 0.52
\]

\[
q_0 = 0.24
\]

F=20%=percent of probable drop of sample

Because there is possibility for decreasing patients due to irregular consumption and withdrawal, number of patients considered 20% more than required (Flow Diagram)

After complete description of the study to the subjects, written informed consent was obtained from each patient. Ethical permission was approved by the Local Ethics Committee of Hamedan University of Medical Sciences. After selecting women suffering PMS, first questionnaire and self assessment were filled out. Women’s self assessment at baseline consisted of the combined scores of the following six symptoms.
related to their at least previous three cycles (headache, nervousness, restlessness, depression, breast swelling and pain, bloating and tympani) with VAS. VAS ranging from 0 (no symptoms) to 10 (unbearable). We chose the scale because it was validated and also because it correlates closely with other more complex tools and is a rapid and straightforward assessment for use in community practice (23). All patients were sent to one specific drugstore to receive a packet containing 3 bottles of either *Vitex agnus* extract or placebo, free of charge. There was a sign in the prescription of those who were in the control group. *Vitex agnus* extract and placebo bottles were produced with identical appearance, and were indistinguishable from each other. The medications were divided into two sets of glass bottles which were labeled: Clinical A and Clinical B. An identification number was noted in a protocol to allow a subsequent identification after the completion of the study and statistical analysis. The information on the placebo and the active substance became available to the investigators and volunteers only after the completion of the study and after the statistical analysis was performed. Patients added 40 drops of *Vitex agnus* or placebo in one glass of fruit juice and drank it before breakfast from the 6th day before menstruation until menstruation, for 6 consecutive cycles. The use of concomitant medications was prohibited.

After 6 menstruation cycles, patients filled out the second questionnaire and self assessment and visited.

Data were analyzed by SPSS 13 software and Wilcoxon signed-rank test was used to determine the effects of the treatment before and after the study in both groups. We used the nonparametric Wilcoxon signed rank test to compare the median of a single column of numbers against a hypothetical median. To compare the two groups, differences in variables before and after the study were calculated and then Mean Ranks were analyzed by Mann-Whitney test because both groups are independent of each other and the responses are continuous measurements.

### Results

The mean ages and, mean duration of PMS, mean cycle length, mean menstruation duration of *Vitex agnus* group (active) and placebo are presented in Table1 which showed no statistically differences. Urban to rural patients’ ratio in each group was approximately 2:1 and regarding literacy, in both groups half of patients finished high school.

Most of the PMS VAS scores were dropped in both groups, however it was more significant in the *Vitex agnus* group ($P<0.0001$). Mean headache, nervousness, restlessness, depression, breast pain and swelling, swelling and tympani of both groups, before and after the treatment, are shown in (Figure 1). Mean Rank of differences of the above variables had significantly difference, before and after the study, in both groups and between two groups ($P<0.0001$) (Table 2). No adverse effect was reported.

### Table 1. Characteristics of 128 women at entry into study of *Vitex agnus* as treatment for the premenstrual syndrome (active treatment, n=62; placebo, n=66)

<table>
<thead>
<tr>
<th></th>
<th>Mean ± SD</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Active</td>
<td>30.77±4.37</td>
<td>NS</td>
</tr>
<tr>
<td>Placebo</td>
<td>30.89±4.02</td>
<td></td>
</tr>
<tr>
<td>Mean days of PMS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Active</td>
<td>5.87±2.24</td>
<td>NS</td>
</tr>
<tr>
<td>Placebo</td>
<td>5.64±1.96</td>
<td></td>
</tr>
<tr>
<td>Cycle length (days)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Active</td>
<td>28±1.2</td>
<td>NS</td>
</tr>
<tr>
<td>Placebo</td>
<td>28±1.0</td>
<td></td>
</tr>
<tr>
<td>Menses duration (days)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Active</td>
<td>4.6±1.0</td>
<td>NS</td>
</tr>
<tr>
<td>Placebo</td>
<td>4.7±0.9</td>
<td></td>
</tr>
</tbody>
</table>
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<table>
<thead>
<tr>
<th>Symptoms</th>
<th><em>Vitexagnus</em></th>
<th>Placebo</th>
<th>P value Mann-Whitney test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>73.54</td>
<td>56.01</td>
<td>0.004</td>
</tr>
<tr>
<td>Nervousness</td>
<td>78.90</td>
<td>50.98</td>
<td>0.000</td>
</tr>
<tr>
<td>Restlessness</td>
<td>79.98</td>
<td>49.96</td>
<td>0.000</td>
</tr>
<tr>
<td>Depression</td>
<td>83.72</td>
<td>46.96</td>
<td>0.000</td>
</tr>
<tr>
<td>Breast swelling &amp; pain</td>
<td>86.73</td>
<td>42.32</td>
<td>0.000</td>
</tr>
<tr>
<td>Bloating and tympani</td>
<td>87.41</td>
<td>42.98</td>
<td>0.000</td>
</tr>
</tbody>
</table>

Figure 1. Mean of basic variables in *Vitex agnus* group and control group before and after treatment

Discussion

The comparison between measured mean ranks of *Vitex agnus* and placebo group showed that there are significant differences in all 6 variables. Several studies confirm our results.

Loch *et al.* studied the effects of *Vitex agnus* on four symptoms of PMS including depression, anxiety, desire for sweets and water blockage (16). They reported 85% decrease of signs in patients (16). Schellenberg studied *Vitex agnus* effects on 6 symptoms (headache, nervousness, mood change, restlessness, breast pain and tympani) in women with PMS in comparison with placebo with successful effects on reducing symptoms (4). Berger *et al.*, studied the effects of *Vitex agnus* effects on 1542 women with PMS from 13 to 62 years. They had prescribed to use 40 drops of *Vitex agnus* for 4 months, every day. In 33% of women all symptoms disappeared and 57% of them were improved (17). Dose of drug in our study was the same as Berger's *et al.*, but the care duration was longer in our study although the number of days of using the drug was fewer.

In another study on 217 women with PMS, prescribing 600 mg *Vitex agnus* 3 times a day had significant effects on reducing mental symptoms but not on water blockage and pain (14). It had contrasted to our study.

In a broad study on 1592 women, including 48 hyper menorrheal, 359 poly menorrheal, 202 secondary amenorrheal, 186 dysmenorrheal, 145 infertility, 175 PMS, 32 irregular menstruations and 66 menorrhagial, were cured by 40 daily drops for 6 months. 60% of them reported that the cure result was good and in 33% of patients all symptoms disappeared and 51% had good
responses to drug (11).

There are several studies which don’t confirm our results. Atmaca et al. compared fluoxetine with Vitex agnus in reducing PSM signs and didn’t observe significant differences between them, but they reported better effects of fluoxetine in curing mental symptoms of PMS (20). Lauritzen et al. compared Vitex agnus by vitamin B6 which had no significant differences between 2 groups (18).

There were two striking differences between our study and the others: we increased duration of treatment (6 months instead of 3), cyclic use instead of daily usage (6 days instead of 30 days), and finally increased Vitex agnus acceptability in spite of its bitterness. Due to the wide acceptance of herbal medicine for management of PMS, their side effects must be considered.

Herbal remedies rarely have side effects and people have more tendencies toward them than chemical therapies. Because in this study the recovery of patients by Vitex agnus was successful, we propose it in management of minor and moderate cases of PMS. Another interesting result of this study was a significant effect of placebo in management of PMS. This finding highlights the effect of mental factors in management of PMS although further studies are needed to investigate this effect.

Acknowledgement

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