

## Evaluation of the efficacy of *Fructus agni casti* in women with severe primary dysmenorrhea: A prospective comparative Doppler study

Ayşe Nur Aksoy<sup>1</sup>, İlay Gözükara<sup>1</sup> and Suna Kabil Kucur<sup>2</sup>

<sup>1</sup>Department of Obstetrics and Gynecology, Nenehatun Hospital, Erzurum, and <sup>2</sup>Department of Obstetrics and Gynecology, Faculty of Medicine, Dumlupınar University, Kütahya, Turkey

### Abstract

**Aim:** The aim of this case–control study was to compare the efficacy of ethinyl estradiol/drospirenone and *Fructus agni casti* in women with severe primary dysmenorrhea measuring uterine artery blood flow via Doppler ultrasonography.

**Methods:** A total of 60 women with severe primary dysmenorrhea and 30 healthy women (control) were included in this study. Thirty patients were treated with ethinyl estradiol 0.03 mg/drospirenone (group 1) and another 30 were treated with *Fructus agni casti* (group 2) during three menstrual cycles. Before and at the end of third month of therapy visual analog scale (VAS) scores, pulsatility index (PI), resistance index (RI) of uterine artery were recorded before and after receiving therapy on the first day of the menstrual cycle.

**Results:** Mean PI and RI values in patients with severe primary dysmenorrhea were significantly higher than in the control groups on the first day of the menstrual cycle ( $P < 0.0001$ ). Mean PI and RI values were significantly lower after the treatment in both groups compared to before values ( $P < 0.001$  for both). After using the drugs for three menstrual cycles, VAS scores were significantly dropped in both groups compared to before treatment values ( $P < 0.0001$  for both); however, there were no significant differences in terms of Doppler findings between group 1 and 2.

**Conclusion:** The effectiveness of *Fructus agni casti* was similar to that of ethinyl estradiol/drospirenone in patients with primary dysmenorrhea.

**Key words:** Doppler ultrasonography, *Fructus agni casti*, oral contraceptive, primary dysmenorrhea, uterine artery.

### Introduction

Primary dysmenorrhea is a menstrual pain on the suprapubic region without any pelvic pathology (e.g. myoma, endometriosis, ovarian cyst). The pain begins just before or on the first day and continues to peak for 3 days of the menstrual cycle. Nausea, vomiting, diarrhea, headache or syncope may occur with pain. The prevalence of primary dysmenorrhea

has been found in 40–90% of women of reproductive age.<sup>1,2</sup> The etiology of primary dysmenorrhea has not been clearly explored. Excessive uterine production of prostaglandin and vasopressin was shown in dysmenorrheic patients.<sup>3,4</sup> They affect myometrial contractility and uterine blood flow. It has been shown that dysmenorrheic patients had significantly higher uterine blood flow indices than healthy controls.<sup>5</sup>

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Reprint request to: Dr Ayşe Nur Aksoy, Department of Obstetrics and Gynecology, Nenehatun Hospital, Erzurum, Turkey.

Email: draysenuraksoy@hotmail.com

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Dysmenorrhea reduces the life-quality of women.<sup>6</sup> Oral contraceptives, acupuncture, *Vitex agnus-castus* extracts such as *Fructus agni casti* and non-steroidal anti-inflammatory drugs such as cyclooxygenase-2 inhibitors are used for treatment of primary dysmenorrhea in women.<sup>4</sup> *Vitex agnus-castus* has been reported to contain essential oils, iridoids, flavonoids, diterpenoids and linoleic acid as an estrogenic compound.<sup>7</sup> Especially in the Mediterranean region of Europe and in Central Asia, it is used to treat female reproductive disorders such as cyclic mastalgia, low fertility, menopause-related complaints, lactation difficulties.<sup>7</sup> Studies have shown that *Vitex agnus-castus* has dopaminergic activity via binding to dopamine-2 receptors.<sup>8</sup> Kilicdag *et al.*<sup>9</sup> compared the effectiveness of *Fructus agni casti* and bromocriptine in hyperprolactinemia and cyclic mastalgia. They found no significant differences between groups for treatment of mastalgia and reduction of prolactin levels. Lauritzen *et al.*<sup>10</sup> compared *Vitex agnus-castus* with pyridoxine in reducing premenstrual syndrome signs and didn't observe significant differences between them. In a recent study,<sup>11</sup> premenstrual syndrome was successfully treated with *Vitex agnus-castus* extract Ze 440 with a dose of 20 mg.

There are many reports regarding dose-dependent anti-oxidant and anti-inflammatory activities of *Vitex agnus-castus* extracts.<sup>12-14</sup> *Vitex agnus-castus* extracts are also used for dropsy, inflammation and as a contraceptive agent in Unani medicine.<sup>15</sup> We hypothesized that if *Vitex agnus-castus* extracts have anti-oxidant and anti-inflammatory activities, *Fructus agni casti* as a *Vitex agnus-castus* extract might affect uterine blood flow in patients with primary dysmenorrhea. Thus, the aim of this study was to compare the efficacy of ethinyl estradiol 0.03 mg/drospirenone 3 mg (Yasmin) and *Fructus agni casti* (Agnucastan) in women with severe primary dysmenorrhea by measuring uterine artery blood flow parameters with color Doppler ultrasonography.

## Methods

The study was approved by the Ethics Committee of the Medical Faculty, Ataturk University. This prospective-randomized study was performed in the Gynecology Department of Nenehatun Hospital. Informed consent was obtained from all subjects before participation. A total of 70 nulliparous women with the diagnosis of severe primary dysmenorrhea were included in this study. Women with regular menstrual cycles (25–30 days), 17–25 years old, nulliparous, non-

smoking, normal ultrasound examination of uterus and adnexa, no chronic inflammatory, circulatory or surgical diseases of the abdomen-pelvis were included. The pain was within 2 or 3 years after menarche, periodical and began a few hours before the menstruation and continued for the first 3 days of the cycle. Those with a body mass index (BMI) of 30 or more, cardiac or pulmonary diseases, endocrine and metabolic diseases, contraindications for the intake of oral contraceptives, alcohol consumption, pelvic pathology (e.g. endometriosis, ovarian cyst, surgery) and using non-steroidal anti-inflammatory drugs were excluded from the study. The control group consisted of 30 nulliparous women without dysmenorrhea.

The visual analog scale (VAS) from 0 (minimum pain) to 10 (maximum pain) was applied to patients on the first day of menstruation.<sup>16</sup> Those with severe dysmenorrhea (7–10 points) were selected for this study ( $n = 60$ ). The VAS scores, age, BMI, menstrual cycle length (day), length of bleeding (day) of patients with severe primary dysmenorrhea were recorded. In the same day, all the patients underwent ultrasound examination to exclude uterine and ovarian pathology, and uterine artery blood flows were measured at the lateral level of uterine artery's cervicocorporeal junction using transabdominal color Doppler ultrasonography at 10.00–12.00 pm. Doppler systole/diastole rates (S/D), pulsatility index (PI) and resistance index (RI) values were recorded. Then, the dysmenorrheic patients were divided into two subgroups ( $n = 35$  for each group). Ethinyl estradiol 0.03 mg/drospirenone 3 mg (Yasmin) was given to group 1, *Fructus agni casti* (Agnucastan) was given to group 2 during three menstrual cycles once a day. Ten patients were discontinued the therapy because of adverse effects. Four patients had spotting, headache, dyspepsia in group 1. Pruritus was recorded in three patients in group 2. Three patients gave up in this study. So, 30 patients continued receiving the drugs in each group. After 3 months of treatment, VAS was again applied to all patients and uterine artery blood flow was measured on the first day of menstruation. The changes in uterine artery blood flow parameters and VAS scores were recorded.

All ultrasonographic scans were performed using the equipment pulse Doppler 5-MHz transabdominal probe (Mindray) for determining the blood flow indices of uterine artery. The uterine artery was visualized at the cervicocorporeal junction. All measurements were made by the same person and three consecutive measurements were calculated.

**Table 1** Sociodemographic data of dysmenorrhea and control groups

	Control	Group 1	Group 2
Age (years)	20.0 ± 1.42	20.6 ± 1.16	20.5 ± 1.30
BMI (kg/m <sup>2</sup> )	23.2 ± 0.96	23.2 ± 0.94	23.2 ± 1.01
Cycle length (days)	28.0 ± 0.69	27.7 ± 0.98	27.6 ± 0.92
Menses duration (days)	5.9 ± 0.66	5.70 ± 0.53	5.73 ± 0.78

Results are given mean ± standard deviation. BMI, body mass index.

By performing a power calculation, when  $\alpha$  error and  $\beta$  error were considered, respectively, as 0.05 and 0.04, with 94% power the patient number for each group was determined as minimum 20. The Statistical Package for Social Sciences for MS Windows (ver. 11.5) was used for data analysis. The data were analyzed to assess the normal distribution with Kolmogorov Smirnov test. As the results did not have a normal distribution, Kruskal–Wallis post-hoc Mann–Whitney *U*-test was used in the comparisons between the groups. For comparison, the Wilcoxon test was applied to the results (VAS scores, Doppler flow parameters) before and after receiving therapy. For all comparisons, the  $P < 0.05$  value was determined as statistically significant.

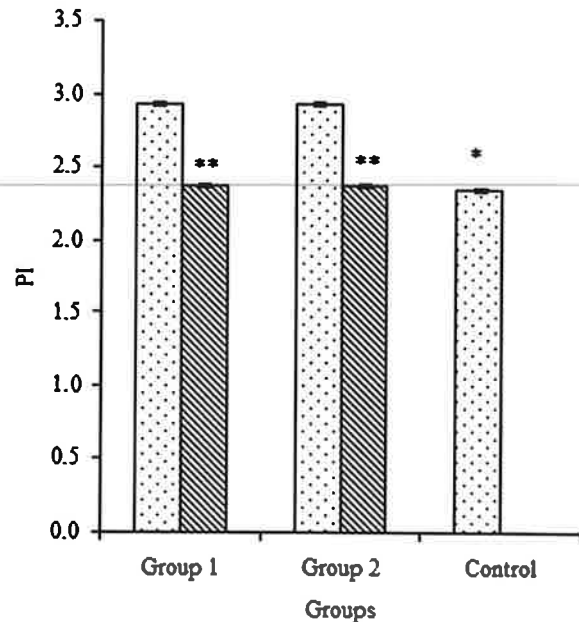
## Results

Sociodemographic data of all patients are presented in Table 1. The mean age, BMI, mean cycle length, menses duration showed no significant differences between groups ( $P > 0.05$ ).

Visual analog scale scores and uterine artery Doppler evaluations of the groups are presented in Figures 1–3 before and after therapy. Mean PI and RI values of the uterine artery blood flow in the control group was found to be significantly lower compared to group 1 and group 2 before therapy ( $P < 0.0001$  for both). After therapy, VAS scores ( $P < 0.0001$ ), uterine artery PI ( $P < 0.0001$ ) and RI ( $P < 0.0001$ ) values were lower than those of before treatment values in group 1. In group 2; also, VAS scores (Fig. 3), uterine artery PI (Fig. 1) and RI (Fig. 2) values decreased after therapy compared to before values ( $P < 0.0001$  for all). After receiving drugs for three menstrual cycles, there were no significant differences between group 1 and group 2 in terms of VAS scores, PI and RI values. Any serious adverse effect was not observed in the groups.

## Discussion

The main finding of our study is that *Fructus agni casti* has similar effects with ethinyl estradiol/drospirenone

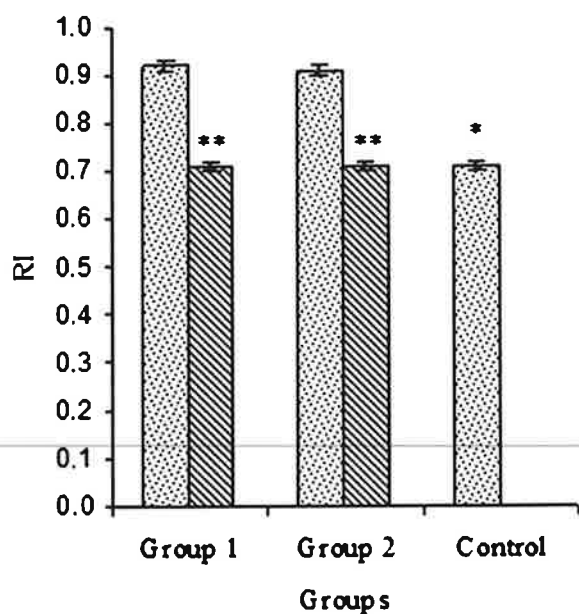


**Figure 1** Pulsatility index (PI) values in all groups. □, before therapy; ▨, after therapy. \* $P < 0.0001$ , compared to group 1 and group 2. \*\* $P < 0.0001$ , compared with before therapy values.

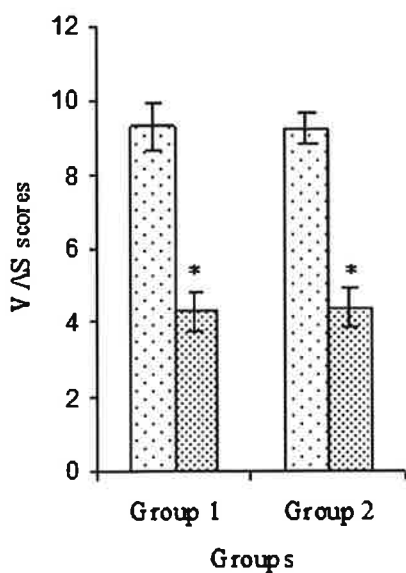
with respect to changing the uterine artery blood flow and reducing menstrual pain.

Dysmenorrhea decreases the quality of life of women. The severe pain negatively affects school and work life.<sup>17–19</sup> Therefore, many interventions such as hormonal contraceptives, non-steroidal anti-inflammatory drugs, diclofenac potassium, *Vitex agnus-castus* extracts have been reported to relieve dysmenorrhea.<sup>4</sup> In this study, we compared the efficacy of *Fructus agni casti* and ethinyl estradiol, an oral contraceptive drug, in pain, RI and PI values in these patient groups.

In the pathology of pain in primary dysmenorrhea it was detected that increasing prostaglandin production and high uterine resistance in uterine arteries.<sup>20</sup> Altunyurt *et al.*<sup>21</sup> reported that dysmenorrheic patients had significantly higher mean PI and RI values in



**Figure 2** Resistance index (RI) values in all groups before and after therapy. □, before therapy; ▨, after therapy. \* $P < 0.0001$ , compared to group 1 and group 2. \*\* $P < 0.0001$ , compared with before therapy values.



**Figure 3** Visual analog scale (VAS) scores in group 1 and group 2 before and after therapy. □, before therapy; ▨, after therapy. \* $P < 0.0001$ , compared to before therapy values.

uterine arteries on the first day of the menstrual cycle than did controls. Royo and Alcazar<sup>22</sup> assessed myometrial vascularization via 3-dimensional power Doppler angiography in patients with primary dysmenorrhea at the moment of maximum menstrual pain. They found increased myometrial vascularization in women with severe dysmenorrhea compared with the control group. In another study, Dmitrovic *et al.*<sup>5</sup> observed significantly higher uterine blood flow indices in dysmenorrheic patients on the first day of the cycle. Similar to their findings; in the present study, the patients with severe primary dysmenorrhea had higher PI and RI values of uterine artery compared to the control group. In contrast to our findings, Celik *et al.*<sup>23</sup> found no significant difference between uterine artery Doppler values of dysmenorrheic and normal women. They found higher Doppler indices at night in patients with primary dysmenorrhea, in comparison to Doppler indices in the daytime. In a study<sup>24</sup> investigating differences in Doppler values among patients with mild and severe primary dysmenorrhea, while significant differences were found in uterine blood flow parameters between mild and severe primary dysmenorrheic patients in large uterine arteries, there were no significant differences in the smaller branches of the uterine artery.

It was shown that oral contraceptives were effective in primary dysmenorrhea by inhibiting ovulation, thickening cervical mucus and decreasing the thickness of the endometrium.<sup>25,26</sup> Previous studies revealed that combined oral contraceptives were a first-line therapy for pain relief from dysmenorrhea for women who want contraception.<sup>3</sup> In our study, VAS scores and Doppler parameters of the uterine artery showed a significant reduction after three menstrual cycles of treatment with ethinyl estradiol/drospirenone in patients with severe primary dysmenorrhea.

*Vitex agnus-castus* extracts were used in female reproductive disorders.<sup>27</sup> Zamani *et al.*<sup>28</sup> studied the effects of *Vitex agnus-castus* on dysmenorrhea symptoms of premenstrual syndrome. After intake of *Vitex agnus-castus* for 4 months, VAS scores dropped more significantly in the *Vitex agnus-castus* group. Prilepskaya *et al.*<sup>29</sup> investigated the efficacy and tolerability of *Vitex agnus-castus* extract in the treatment of patients with premenstrual syndrome. They found that *Vitex agnus-castus* extract was an effective and well-tolerated drug in the treatment of moderate and severe premenstrual syndrome without any serious adverse events. In a recent study, Schellenberg *et al.*<sup>11</sup> demonstrated that *Vitex agnus-castus* extract was beneficial in relieving symptoms of premenstrual syndrome. In our

study, VAS scores and Doppler parameters of uterine artery decreased significantly in the *Fructus agni casti* group similar to the ethinyl estradiol/drospirenone group. The mean PI and RI values for the uterine arteries in the two groups were significantly lower than before the treatment. VAS scores were dropped in both groups, although there was no significant difference between the two groups.

To the best of our knowledge, no study in the published work has compared the efficacy of ethinyl estradiol-drospirenone and *Fructus agni casti* by inspection of uterine blood flow alterations in women with severe primary dysmenorrhea. Ibrahim *et al.*<sup>30</sup> researched gynecological efficacy and chemical content of *Vitex agnus-castus* L. Fruits. They found that the administration of chaste tree extract to ovariectomized rats induced estrogenic-like effect with a typical and predictable estrogenic response. Jarry *et al.*<sup>31</sup> reported that flushes and vaginal dryness in postmenopausal women were prevented by *Vitex agnus-castus* extracts. On the other hand, it was showed that *Vitex agnus-castus* extract induces significant reduction in plasma prolactin levels<sup>9</sup> and prolactin affects the actions of estrogen in the uterus.<sup>32</sup> *Vitex agnus-castus* extracts also have anti-oxidant and anti-inflammatory activities.<sup>13</sup> These data may partially explain why *Vitex agnus-castus* affects uterine blood flow.

Several limitations of our study should be recognized. The first one was a lack of long-term follow up of the patients. The second major drawback was that the patient population was relatively small. Our results need to be confirmed in larger prospective studies.

As a result, it may be suggested that the effectiveness of *Fructus agni casti* was similar to ethinyl estradiol/drospirenone in patients with primary dysmenorrhea. Both drugs are well tolerated and provide effective relief of dysmenorrhea. Therefore, both drugs may appear to be an appropriate choice for the treatment of pain in patients with primary dysmenorrhea. More comprehensive studies may be conducted to reveal the effectiveness of *Fructus agni casti* in the control of pain caused by dysmenorrhea.

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