Effect of French Maritime Pine Bark Extract on Endometriosis as Compared with Leuprorelin Acetate

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OBJECTIVE: To clarify the effect of Pycnogenol (Horphag Research, Geneva, Switzerland), French maritime pine bark extract, on endometriosis.

STUDY DESIGN: Fifty-eight women were included in this study. They were operated on conservatively for endometriosis and surgically diagnosed with the condition. All patients were followed at 4, 12, 24 and 48 weeks after starting treatment to check for endometriosis signs and symptoms, including changes in CA-125 and estrogen levels (E_2). Thirty-two patients in the Pycnogenol treatment group took 60 mg Pycnogenol orally a day for 48 weeks. The 26 patients who received gonadotropin-releasing hormone agonist (Gn-RHa) were treated in the standard way.

RESULTS: Treatment with Pycnogenol slowly but steadily reduced the symptom scores. Treatment with Gn-RHa reduced the scores more efficiently; however, 24 weeks after the end of treatment, the scores suggested a recurrence of signs. No influence of treatment on menstrual cycles or E_2 was observed in the Pycnogenol group. CA-125 decreased in both treatment groups. Patients with smaller endometriomas responded better to treatment as compared to patients with larger endometriomas. In the Gn-RHa group, the lowering of CA-125 concentrations was far more pronounced; however, a clear rebound effect was observed.

CONCLUSION: Pycnogenol is a therapeutic alternative to Gn-RHa in the treatment of endometriosis. (J Reprod Med 2007;52: 703–708)

This study demonstrated the suppressive effects on all symptoms of endometriosis—dysmenorrhea, pelvic pain, pelvic tenderness and induration—with long-term treatment with Pycnogenol.

Keywords: endometriosis, gonadotropin-releasing hormone, Pycnogenol, French maritime pine bark extract.

Endometriosis is a disease of ectopic occurrence and growth of endometrium in the ovary, oviduct and pouch of Douglas. The disease causes inflammation at the site and development of severe menstrual and lower abdominal pain at times other than the menstrual period.[1] The disease is most prevalent between the ages of 18 and 42. Because of its dependence on follicular hormones (estrogens), the disease increases gradually in menstruating women and decreases and disappears postmenopausally because of the reduced production of estrogens.[2]

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Financial Disclosure: The authors have no connection to any companies or products mentioned in this article.

0024-7758/07/5208-0703/$15.00/0

Gonadotropin-releasing hormone agonists (Gn-RHas) are the most commonly used drugs for treating severe dysmenorrhea complicated by endometriosis and/or adenomyosis. Dysmenorrhea often relapses after cessation of Gn-RHa therapy, especially in younger patients, and during Gn-RHa therapy patients cannot become pregnant. Cyclic administration of contraceptive hormones may have some effect on prevention of recurrence of endometriosis or adenomyosis after Gn-RHa therapy but is not applicable to patients who want to become pregnant.[3]

Endometriosis may be treated with a danazol testosterone derivative for inhibiting the estrogenic activity of the lesion.[4] However, this therapy frequently produces side effects, including symptoms of ovarian deficiency, such as hot flushes and systemic malaise, osteoporosis, edema and obesity, due to the anabolic and androgenic side effects.[5] Also, with danazol, patients up to the age of 40 have an endometriosis recurrence rate of 80% 3–6 months after the completion of treatment.

Pycnogenol (Horphag Research, Geneva, Switzerland), a standardized extract from the bark of the French maritime pine, has been shown to possess antiinflammatory action by inhibiting the production of a number of inflammatory mediators.[6] Some of the components of Pycnogenol acted in animal experiments as spasmolytic agents. Treatment with Pycnogenol showed good efficacy in treating menstrual cramps and pain in our clinical trials. In 1 investigation, women with severe menstrual pain and endometriosis showed a high response rate (71–100%) after supplementation with Pycnogenol.[7] In another clinical trial with patients complaining of dysmenorrhea, we could observe a significant alleviation of abdominal and lower back pain ($p < 0.01$). Patients reported fewer days of pain, and use of analgesics dropped.[8] These previous studies revealed that Pycnogenol has an efficient suppressive effect on menstrual pain.

Because of these positive experiences, we choose Pycnogenol as a safe, natural product to treat pregnancy-associated pain.[9] We investigated the potential of Pycnogenol in comparison with the Gn-RHa leuprorelin acetate on symptoms associated with surgically and clinically diagnosed endometriosis.

Patients and Methods

Patients

From 1999 to 2004, 58 women participated in this study, their ages ranging from 21 to 38 years (mean, 33.2 ± 4.0). They had undergone conservative operations for endometriosis within the previous 6 months. They were surgically diagnosed in accordance with Revised American Fertility Society (R-AFS) classification: stage II, 22 cases; stage III, 28 cases; and stage IV, 12 cases. The patients refused to undergo further surgery and were diagnosed in our outpatient clinic as having recurrent moderate to severe dysmenorrhea or other pelvic pain or disorders. Patients gave informed consent prior to the study and could leave the study at any time.

Table I *Scores of Symptoms and Findings in Patients with Endometriosis*

Symptoms and findings	Degree	Criteria	Points
Menstrual pain	Severe	Analgesics are minimally or not effective. Daily life with some absence from work.	3
	Moderate	Analgesics relieve pain, with little effect on daily life.	2
	Mild	Few or no analgesics are taken.	1
	Nil	/	0
Pelvic pain	Severe	Requires strong analgesics. Persistent during cycle other than during menstruation.	3
	Moderate	Noticeable discomfort for most of cycle.	2
	Mild	Occasional pelvic discomfort.	1
	Nil	/	0
Pelvic tenderness	Severe	Unable to palpate because of tenderness.	3
	Moderate	Extensive tenderness on palpation.	2
	Mild	Minimal tenderness on palpation.	1
	Nil	/	0
Induration	Severe	Nodular adnexa and cul-de-sac, uterus frequently frozen.	3
	Moderate	Thickness and indurated adnexa and cul-de-sac, restricted uterine mobility.	2
	Mild	Uterus freely mobile, induration in cul-de-sac.	1
	Nil	/	0

Methods

After confirming regular menstruation and ovulation with the basal body temperature (BBT) for 3 months before treatment, the patients were examined before and at 4, 12, 24 and 48 weeks after starting treatment to check for symptom control (pain score and urinary and bowel symptom scores), breakthrough bleeding and side effects of the medication. Pain was evaluated by patients' self-assessment score of the severity of dysmenorrhea and pelvic pain since their previous visit. The investigator interviewed and performed a gynecologic examination on each patient. Symptoms were scored according to Table I. The smear test examination of the uterine cervix, ultrasonography, magnetic resonance imaging and serologic hormonal examinations of all patients, including CA-125 and estradiol in the middle of the proliferative phase, were performed before treatment.

Treatment

Patients were randomized to 2 groups: Pycnogenol or Gn-RHa.

Patients in the Pycnogenol group took 30 mg Pycnogenol orally as capsules twice a day (total, 60 mg) for 48 weeks immediately after morning and evening meals. Treatment started on the eighth day of the menstrual cycle after reporting pain scores during a whole cycle before treatment. If a patient did not take the prescribed amount of capsules on a certain day, she was instructed to increase the dosage accordingly on the next day. The patients did not take psychotropic drugs, vitamins or Chinese kampo medicines during treatment with Pycnogenol. Also, physical therapy could not be introduced during the study period. Laxatives and medications necessary to continue with existing therapy were allowed. The use of analgesics was not restricted during the study; however, the dosage and type of analgesic had to be reported to a physician. The patients kept BBT charts during observation. If symptom control was unsatisfactory or side effects became significant, the patient could choose to terminate the medication or switch to another therapy.

The patients who received Gn-RHa therapy received injected leuprorelin acetate depot, 3.75 mg intracutaneously, 6 times every 4 weeks.[10] Add-back therapy, hormonal replacement with Premarin (Wyeth Medica Ireland, Newbridge, Co. Kildare, Ireland), 1.25 mg/d, during Gn-RHa treatment was performed if necessary.[11] After 6 treatments with Gn-RHa, patients did not receive other hormonal therapy. The patients were supposed to start checking their BBT at the onset of menstruation after the last treatment with Gn-RHa during observation.

Statistical Evaluation

Data are represented as mean ± SD and were evaluated by Wilcoxon rank sum test with Bonferoni correction using the sum of the scores for each symptom or by paired Student *t* test for serologic examination.

Results

The characteristics of the treatment groups showed no differences at the start of treatment:

In the Pycnogenol group, 32 patients were included (mean age, 33.6 ± 4.1 years; range, 24–39).

Table II *Changes in Scores During Treatment with Pycnogenol and Gn-RHa*

	Menstrual pain		Pelvic pain		Pelvic tenderness		Pelvic induration	
	P	G	P	G	P	G	P	G
Before	3.3 ± 0.75 (n = 32)	3.0 ± 0.72 (n = 26)	3.2 ± 0.68 (n = 31)	3.1 ± 0.74 (n = 26)	3.3 ± 0.60 (n = 32)	3.2 ± 0.70 (n = 26)	3.1 ± 0.66 (n=32)	3.0 ± 0.75 (n = 26)
4 Wk	2.8 ± 0.77** (n = 32)	2.0 ± 0.80 (n = 4)	2.8 ± 0.88 (n = 31)	2.4 ± 0.70** (n = 26)	2.9 ± 0.73* (n = 32)	2.3 ± 0.74** (n = 26)	2.8 ± 0.78* (n = 32)	2.5 ± 0.65** (n = 26)
12 Wk	2.3 ± 0.65** (n = 30)	/	2.4 ± 0.82** (n = 29)	1.6 ± 0.77**,**** (n = 25)	2.4 ± 0.56** (n = 30)	2.0 ± 0.89**,**** (n = 25)	2.2 ± 0.70** (n = 30)	1.6 ± 0.65**,*** (n = 25)
24 Wk	2.4 ± 0.65** (n = 24)	/	2.3± 0.76** (n = 23)	0.95 ± 0.22**,**** (n = 20)	1.9 ± 0.93** (n = 24)	2.1± 0.69 ** (n=20)	2.1± 0.61 ** (n = 24)	0.95 ± 0.39**,**** (n = 20)
48 Wk	2.2 ± 0.59** (n = 24)	2.3 ± 0.66** (n = 20)	2.1 ± 0.63** (n = 23)	2.5 ± 0.89*,***** (n = 20)	2.2 ± 0.45** (n = 24)	2.8 ± 0.97**,***,***** (n = 20)	2.1 ± 0.58 ** (n = 24)	2.4 ± 0.68**,***** (n = 20)

*p < 0.05 and **p < 0.01 as compared with before treatment. ***p < 0.05 and ****p < 0.01 as compared with P group.
*****p < 0.01 as compared with 24 weeks of treatment.
P = Pycnogenol, G = Gn-RHa.

Table III *Changes in Serum CA-125 During Treatment with Pycnogenol and Gn-RHa*

	CA-125 (U/mL)			
	Pycnogenol		Gn-RHa	
Size of endometriomas	< 2 cm	≥ 2 cm	< 2 cm	≥ 2 cm
Before	64.6 ± 27.6 (n = 32)		77.9 ± 44.7 (n = 26)	
	56.9 ± 16.3 (n=12)	69.5 ± 34.4 (n=20)	69.4 ± 20.3 (n=10)	83.2 ± 54.8 (n=16)
4 Wk	57.0 ± 25.8 (n = 32)		61.5 ± 42.5 (n = 26)	
	44.1 ± 17.9 (n=12)	65.2 ± 28.4 (n=20)	59.6 ± 28.0 (n=10)	62.7 ± 50.3 (n = 16)
12 Wk	49.1 ± 27.1 (n = 30)		24.5 ± 26.0**** (n=25)	
	31.6 ± 12.7** (n = 10)	62.7 ± 29.2 (n = 14)	19.3 ± 9.2 **,*** (n = 10)	28.0 ± 32.7**,**** (n = 15)
24 Wk	48.5 ± 27.5 (n = 24)		16.4 ± 7.7**** (n =20)	
	34.6 ± 9.6** (n = 10)	62.3 ± 32.6 (n=14)	15.4 ± 5.7**,**** (n =10)	17.3 ± 9.6**,**** (n = 10)
48 Wk	43.3 ± 19.1 (n = 24)		69.6 ± 24.3**** (n = 20)	
	35.2 ± 6.9** (n = 10)	55.7 ± 18.1* (n=14)	75.3 ± 23.1****,***** (n = 10)	63.8 ± 25.2***** (n = 10)

*p < 0.05 and **p < 0.01 as compared with before treatment. ***p < 0.05 and ****p < 0.01 as compared with P group.
*****p < 0.01 as compared with 24 weeks-treatment.

Endometriosis was surgically diagnosed as stage II in 12 cases, stage III in 14 cases and stage IV in 6 cases according to the R-AFS.

In the Gn-RHa group 26 patients were included (mean age, 32.8 ± 3.8 years; range, 21–38). Endometriosis was diagnosed as stage II in 10 cases, stage III in 10 cases and stage IV in 6 cases.

In the Pycnogenol group, 3 patients stopped treatment after 8 weeks; after 16 weeks, 2 patients requested another treatment. Of the remaining 29 patients, 5 became pregnant (after 4–12 weeks, 2 cases; after 12–24 weeks, 3 cases). Their data before they left the study were used for statistical evaluation.

In the Gn-RHa group, 5 patients stopped therapy due to general malaise after 12 weeks of treatment and 1 patient stopped therapy because of prolonged, massive uterine bleeding after 8 weeks of treatment.

Patients in both groups reported severe pain, pelvic tenderness and pelvic indurations at the start of treatment (Table II). Treatment with Pycnogenol slowly but steadily reduced all the symptom scores from severe to moderate (Table II). Treatment with Gn-RHa reduced the scores more efficiently; however, 24 weeks after the end of treatment the scores demonstrated the recurrence of symptoms (Table II).

As expected, Gn-RHa suppressed menstruation during treatment, whereas in the Pycnogenol group no influence of treatment on menstrual cycles was observed. Gn-RHa lowered estrogen levels drastically; in contrast, the estradiol values of the Pycnogenol group showed no systematic changes over the observation period.

The values of serum marker CA-125 for endometriosis decreased in both treatment groups (Table III). Patients with smaller endometriomas responded better to treatment as compared to patients with large endometriomas. The lowering of CA-125 concentrations was by far more pronounced in the Gn-RHa group; however, a clear rebound effect was observable in the Gn-RHa group in contrast to the Pycnogenol group, where values remained at a lower level (Table III).

Side effects observed in the Pycnogenol group were mild and transient, none of the patients left the study because of side effects. The most frequently report unwanted effect was dysfunctional uterine bleeding (8), followed by epigastralgia (6), increase in menstrual bleeding (6) and acne (5). Two patients reported 3 symptoms simultaneously; 6 patients reported 2 symptoms; 17 patients reported no unwanted effects.

In the Gn-RHa group, hot flushes (22), general malaise (18) and lumbago (12) were reported. Five patients reported general malaise stopped treatment because of its severity. Add-back therapies had to be prescribed in 8 cases of general malaise after the last treatment with Gn-RHa. The period from last treatment with Gn-RHa to onset of first menstruation was 13.2 ± 2 weeks and of first ovulation, 11.4 ± 2.2 weeks.

Discussion

Endometriosis is estimated to affect 2–3% of the

general female population and may cause dysmenorrhea, dyspareunia, chronic pelvic pain, and primary or secondary infertility.[12,13] Endometriotic implants tend to regress in a hypoestrogenic environment.[14,15] That has brought the development of several medical antigonadotropic and antiestrogenic treatments for endometriosis. Because of their anabolic and androgenic side effects, danazol and the progestogens have been replaced by the Gn-RH analogs.[16] This treatment is conducted usually for 6 months, effectively alleviating or eliminating menstrual pain due to endometriosis and pain from other causes. However, symptoms of ovarian deficiency appear with high frequency during treatment, seriously impairing the quality of life. Moreover, the incidence of subsequent recurrence of endometriosis is extremely high after treatment. Because of the risks of these hormonal treatments, there is a need for effective treatment of endometriosis without long-lasting adverse effects.

We reported the short-term effect of Pycnogenol on dysmenorrhea.[9] This study demonstrated the suppressive effects on all symptoms of endometriosis—dysmenorrhea, pelvic pain, pelvic tenderness and induration—with long-term treatment with Pycnogenol. The efficacy of Pycnogenol in treating endometriosis by reducing pelvic pain, tenderness and induration confirmed our previous reports of the positive effect of Pycnogenol for endometriosis.[8]

CA-125 is a good predicting marker for the evaluation and treatment of advanced endometriosis in patients with an initially elevated CA-125 level.[17] CA-125 is a glycoprotein with a molecular weight of approximately 200 kd expressed on the cell surface of some derivatives of celomic epithelium. According to Barbieri et al,[18] 2 mechanisms may be responsible for elevated blood levels of CA-125 in endometriosis. First, endometriotic lesions appear to have a greater membrane concentration of CA-125 as compared to normal endometrium. Second, the local inflammation associated with endometriosis may increase the rate at which CA-125 is shed from the membranes of endometriotic lesions into the circulation. Inflammation-induced leakage of capillary endothelium could also explain why serum CA-125 increases in patients with acute pelvic inflammatory disease. As for the changes in CA-125 during treatment with Pycnogenol, it is possible that the antiinflammatory effects of Pycnogenol[6] decrease the serum content of CA-125 in patients with small endometrial cysts. However, only a small decrease in CA-125 was observed in patients with large cysts due to the fact that endometrial cysts were filled with CA-125.[19-21]

The reduction of symptoms could be the result of the combined action of the constituents of Pycnogenol, which contains a number of phenolic acids.[22] Two of them, ferulic and caffeic acid, have a spasmolytic effect on the isolated uteri of rats.[23] Ferulic acid especially can inhibit uterine contractions in rodents in vivo. These constituents of Pycnogenol, perhaps together with other phenolic acids in Pycnogenol, could be responsible for the relief from cramping pain. Recently a close relationship was demonstrated between reactive oxygen species and endometriosis.[24] Pycnogenol shows strong free radical–scavenging activity against reactive oxygen and nitrogen species[25]; that indicates that its antioxidant capacity could also cause an improvement in endometriosis, especially long-term treatment.

During treatment with Gn-RHa, estradiol in all patients was extremely lowered by the reduction of ovarian function, the main mechanism to inactivate endometrial cells due to their estrogen dependency. The result is a reduction in inflammatory changes inside the tissues that cause several symptoms of endometriosis. However, this deactivated ovarian function quite frequently causes adverse effects, such as hot flushes, general malaise or loss of bone mineral. The profound hypoestrogenism is an inherent disadvantage of treatment with Gn-RHa.[11] Moreover, after the end of treatment with Gn-RHa, estradiol levels increase rapidly around 3 months after the end of the therapy, causing recurrence of endometriosis, as demonstrated in this study by the increase in scores of pelvic pain, tenderness and induration after the end of treatment. In contrast, Pycnogenol treatment did not reduce estradiol, so endometriosis patients never lost the normal hormonal milieu.

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