

# Historical prospective cohort study of the recurrence of pain after discontinuation of treatment with danazol or a gonadotropin-releasing hormone agonist

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**Objective:** To determine the duration of time to the recurrence of pain attributable to endometriosis after the discontinuation of treatment with danazol or a GnRH agonist (GnRH-a) in patients who have had a satisfactory response to the treatment.

**Design:** Retrospective study.

**Setting:** Nine academic medical centers in three countries.

**Patient(s):** Three hundred twenty-seven women with diagnosed and staged endometriosis who were treated with at least 6 months of danazol or a GnRH-a and who experienced significant pain relief with therapy.

**Intervention(s):** None.

**Main Outcome Measure(s):** Duration of pain relief after completion of treatment as determined by a patient-initiated report of pain recurrence or increase in pain severity requiring intervention.

**Result(s):** The median time to the recurrence of pain was 6.1 months for patients treated with danazol and 5.2 months for patients treated with a GnRH-a.

**Conclusion(s):** Although there was a lack of uniformity in treatment effects across sites, the analyses have taken into account major covariant effects. The time to the recurrence of endometriosis-associated pain after danazol treatment was slightly longer than that after GnRH-a treatment. (Fertil Steril® 0;70:293-6. ©1998 by American Society for Reproductive Medicine.)

**Key Words:** Endometriosis, danazol, GnRH agonist, pain recurrence, efficacy

Endometriosis affects  $\geq 10\%$  of women of childbearing age and represents a significant physical and financial burden. Further, endometriosis is one of the more common causes of pelvic pain in this age group. Pain associated with endometriosis varies in type, severity, and constancy and can include dysmenorrhea, dyspareunia, nonmenstrual pelvic pain, and pelvic tenderness.

The medical treatment of endometriosis with either danazol or a GnRH agonist (GnRH-a) has been shown to reduce both the observable number of endometriotic implants and the frequency and severity of associated pain (1-5). Numerous prospective trials have

been reported that compared the safety and efficacy of danazol and GnRH-a therapy for endometriosis. The results of these studies have shown both treatments to be equally safe and efficacious in reducing the number of endometriotic implants (1-6). Further, both danazol and the GnRH-a provide a statistically equal reduction in endometriosis-related pain during drug therapy (1-6).

Reanalysis by  $\chi^2$  of results previously reported in the literature (4) has shown statistically significant differences in the incidence of pelvic pain and pelvic tenderness in individuals treated with danazol versus the GnRH-a leuprolide acetate. The issue of frequency and

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TABLE 1

Uniform definitions of endometriosis-associated pain.

Pain type	Pain score*	Definition
Dysmenorrhea	0	No discomfort
	1	Slight interference with usual activities of daily living; none to occasional use of nonnarcotic analgesics or NSAIDs
	2	Noticeable interference in activities of daily living; regular use of nonnarcotic analgesics or NSAIDs
	3	Extreme interference with activities of daily living; unable to function normally; requires narcotic analgesics
Dyspareunia	0	No discomfort
	1	Tolerated discomfort
	2	Pain to the point of interruption of intercourse
	3	Avoids intercourse because of pain
Pelvic pain (not menstrual or coital)	4	Not sexually active
	0	No discomfort
	1	Occasional pelvic discomfort or premenstrual pain; occasional use of nonnarcotic analgesics or NSAIDs
	2	Discomfort during most of cycle; regular use of nonnarcotic analgesics or NSAIDs
	3	Constant pain; narcotic analgesics required

\* NSAIDs = nonsteroidal anti-inflammatory drugs; 0 = absent; 1 = mild; 2 = moderate; 3 = severe.

rapidity of pain recurrence is of importance in determining the relative effectiveness of medical alternatives for the treatment of endometriosis. Accordingly, this study was initiated in nine academic medical centers to determine the time to pain recurrence after treatment with danazol versus a GnRH-a.

## MATERIALS AND METHODS

Of the nine centers that participated in this study, eight of the applicable institutional review boards determined that institutional review board approval of the study was not required because no experimental therapies were being administered and the study consisted only of documentation of therapeutic effect. The study received institutional review board approval at the ninth center. Nine academic medical centers in three countries submitted data on 327 patients who had laparoscopically diagnosed and staged endometriosis and associated pelvic pain. The data were collected retrospectively by review of patient chart documentation from the nine academic centers.

A revised American Fertility Society (AFS) endometriosis (7) score was determined at the time of staging laparoscopy. Some patients had had medical or surgical interventions before the staging laparoscopy and before baseline pain assessments were determined. Data on prior interventions were not gathered; however, no interventions were allowed between the staging laparoscopy and baseline pain assessment and the initiation of the documented medical endometriosis therapy.

The degree of pain was assessed by patients before medical treatment, at the completion of 6 months of medical treatment, at the time of the first posttreatment menstruation, and at the time of pain recurrence requiring intervention. The

definitions of pain severity for dysmenorrhea, dyspareunia, and nonmenstrual, noncoital pelvic pain are listed in Table 1.

All patients had been treated with either danazol or a GnRH-a for at least 6 months with approved doses. Danazol was administered in daily doses of 400 mg to 800 mg. Patients treated with a GnRH-a received either buserelin acetate, (Hoechst-Roussel, Germany), nafarelin (Synarel; Searle, Skokie, IL), goserelin acetate (Zoladex; Zeneca Pharmaceuticals, Wilmington, DE), or leuprolide acetate (Lupron Depot; TAP Pharmaceuticals, Bannockburn, IL) in approved doses. A single patient who received triptorelin (Decapeptyl; Wyeth-Ayerst, Radnor, PA) was not included in the analyses.

The medical treatment of each patient had resulted in either complete elimination of pain or a significant improvement from baseline pain levels. Significant improvement was defined either as improvement as judged by patient assessment of two or more levels in the severity of any pain type or as qualitative improvement in pain (i.e., better or much better) when severity scores had not been obtained. Degree of pain for quantitative analysis was defined carefully and uniformly across all sites and for each pain type (dysmenorrhea, dyspareunia, nonmenstrual pelvic pain, and pelvic tenderness).

To avoid selection bias, attempts were made to collect data on all patients who met the inclusion criteria, including those who were lost to follow-up. Direct contact was made with patients for clinical review when necessary.

Patients who had other medical conditions that could be responsible for their pain were excluded from analysis, as were patients who had surgical treatment of endometriosis during the diagnostic laparoscopy, the posttreatment laparoscopy, or any time between the posttreatment laparoscopy and the report of pain recurrence. Also excluded from anal-

TABLE 2

Demographic and baseline characteristics of the 264 patients whose cases were analyzed.

Characteristic	Treatment group		Total (n = 264)
	Danazol (n = 94)	GnRH agonist (n = 171)	
Age (y)			
Mean $\pm$ SD	34.6 $\pm$ 7.5	34.2 $\pm$ 7.4	34.4 $\pm$ 7.4
Median (range)	35.4 (19.0–49.6)	34.4 (12.5–49.6)	34.8 (12.5–49.6)
Time from endometriosis diagnosis to treatment start (y)			
Mean $\pm$ SD	1.6 $\pm$ 2.7	1.4 $\pm$ 2.3	1.4 $\pm$ 2.4
Median (range)	0.1 (0–12)	0.2 (0–12)	0.2 (0–12)
No. (%) with revised AFS disease stage			
I	34 (37)	43 (27)	77 (30)
II	29 (32)	73 (42)	102 (40)
III	16 (18)	28 (17)	44 (17)
IV	12 (13)	23 (14)	35 (14)

ysis were patients who had physician-initiated hormonal treatment of endometriosis or of infertility after the completion of danazol or GnRH-a therapy but before the patient's report of pain recurrence, and patients who had become pregnant.

The end of medical therapy was defined as the last day of dosing for oral or intranasal products or 30 days after the last dose of a depot product. The interval from the end of medical endometriosis therapy to the patient-initiated report of either the recurrence of pain associated with endometriosis or an increase in the qualitative assessment of pain (worse or much worse) requiring medical or surgical intervention was determined. This interval was called the "pain-free interval" and was the primary end point of the study.

Time-to-event analysis (survival analysis) was used to estimate and test for treatment differences in pain-free interval. The survival distribution for pain-free interval was estimated using the Kaplan-Meier method, and treatment groups were compared by the log-rank test. In addition, potential covariates such as age, AFS stage (7), add-back therapy, dysmenorrhea at recurrence of first menses, time of onset of first menses, and treatment duration were assessed for any effects on pain-free interval.

A censored time-to-pain recurrence was included in the analysis and contributed to the median estimation of pain recurrence but was not counted as an end point event. A Cox model survival analysis was used to study the relative importance of these covariates and to provide adjusted treatment group *P* values in the presence of covariates.

## RESULTS

### Demographics

Data were collected on 327 patients for this study; 128 had received danazol and 199 had received a GnRH-a. The

mean patient age at the initiation of medical treatment was 34 years in the danazol group and 35 years in the GnRH-a group. The mean time from the diagnosis of endometriosis to the initiation of medical treatment was 1.4 years in both groups and ranged from <1 year to 12 years in both groups. The revised AFS score at the time of the initial laparoscopy was comparable between the two groups, although more patients had stage I disease in the danazol group (37%) than in the GnRH-a group (27%), whereas more patients had stage II disease in the GnRH-a group (42%) than in the danazol group (32%). The percentage of patients with stage III and IV disease was identical in the two groups.

Of the 327 patients, 264 had information that was complete, and these were included in the pain-free interval analysis. The demographic characteristics of the analyzed patients are given in Table 2.

### Time to Pain Recurrence

Twenty-six of the 264 patients included in the analysis had received add-back therapy during their medical treatment of endometriosis. The median time to pain recurrence was 2.6 months among the patients who received add-back therapy compared with 5.2 months among those who did not (*P* = 0.08). To minimize bias in the comparisons of the danazol and GnRH-a groups, the patients who received add-back therapy were excluded from further analysis. Comparison of the time to pain recurrence for those patients who did not receive add-back therapy revealed an approximate 4-week advantage for danazol (median 6.1 months) compared with the GnRH-a (median 5.2 months) and was statistically significant (*P* = 0.03).

As expected, the time to pain recurrence varied with the stage of endometriosis. For patients who had been treated with danazol, the median time to pain recurrence for those

TABLE 3

Time to pain recurrence: covariate analysis.

Covariate	Median (mo)	95% Confidence interval
Dysmenorrhea		
Danazol	4.6	(2.9–5.8)
GnRH agonist	3.7	(3.3–5.5)
No dysmenorrhea		
Danazol	7.2	(6.4–10.1)
GnRH agonist	6.7	(6.2–9.9)
Add-back therapy		
Danazol	Insufficient data	
GnRH agonist	3.4	(2.5–4.8)
No add-back therapy		
Danazol	6.1	(5.0–7.1)
GnRH agonist	5.2	(4.9–6.4)

with stage I and II disease was 6.0 months (95% confidence interval [CI]: 5.0–7.2). For danazol-treated patients with stage III and IV disease, the median time to pain recurrence was 6.3 months (95% CI: 3.1–10.8). For patients who had been treated with a GnRH-a, the median time to pain recurrence was 5.3 months for those with stage I and II disease (95% CI: 3.7–6.0) and 5.9 months for those with stage III and IV disease (95% CI: 3.9–6.8).

In the combined site analysis, covariates were assessed for a number of prognostic variables to identify any potential correlation with time to pain recurrence. These are summarized in Table 3. Dysmenorrhea at first menstruation after therapy was associated with a shorter time to pain recurrence for both the danazol and GnRH-a groups, although the danazol group had a longer time to recurrence regardless of whether dysmenorrhea occurred. The danazol group exhibited a consistent time to pain recurrence when analyzed according to patient age, whereas the GnRH-a group showed better results in older patients. Both groups had a longer time to pain recurrence when therapy was extended beyond 6 months.

For danazol-treated patients, the time to pain recurrence also was analyzed for those who received an 800-mg daily dose ( $n = 43$ ) versus those who received a daily dose of <800 mg ( $n = 46$ ). No statistically significant difference between these two dosing groups was found. The median time to recurrence of pain was 6.1 months in each group.

Differences were seen in the time to pain recurrence when various GnRH-a were used. These differences were not statistically significant.

## DISCUSSION

Ideal therapy for endometriosis would result in permanent relief of endometriosis-associated pain. No current treatment

of endometriosis—medical, surgical, or combined—provides this ideal outcome. In the absence of the ideal therapy, physicians should use evidence-based medicine to select treatments that provide the greatest benefit at the lowest cost.

The cases of 327 patients were reviewed for this study; 128 received danazol therapy and 199 received a GnRH-a. Two hundred sixty-four patients satisfied the required criteria for analysis of pain-free interval; 94 received danazol and 170 received a GnRH-a. A greater percentage of danazol-treated patients had stage I endometriosis (37%) than did GnRH-a-treated patients (27%). More GnRH-a-treated patients than danazol-treated patients had stage II disease (42% versus 32%). The proportion of patients with stage III and IV endometriosis was identical across the treatment groups.

When the 26 patients who received a GnRH-a plus hormonal add-back therapy were compared with those who received a GnRH-a alone, an advantage was found for the latter group. To minimize bias, patients who received add-back therapy were not included in further analysis.

Differences in therapeutic efficacy as measured by time to pain recurrence were found between the four GnRH-a used in this study. However, these differences were not statistically significant.

Although there were differences in treatment effects across sites, the analyses conducted have taken into account major covariate effects. The results of stratified analysis and adjustment of treatment effects in the presence of these covariates indicate that danazol therapy provides an equal or longer pain-free interval from endometriosis-associated pain than do GnRH-a. The combined site analysis resulted in an approximate 4-week advantage for danazol (median 6.1 months) compared with GnRH-a (median 5.2 months), and the difference is statistically significant ( $P = 0.03$ ). Although the difference is statistically significant, a 4-week difference probably is not clinically relevant. The rapidity of pain recurrence is disappointing in both treatment groups.

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