Depot leuprorelin acetate versus danazol in the treatment of infertile women with symptomatic endometriosis

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Summary

Purpose of investigation: Endometriosis is a common finding in women with infertility, but the mechanism by which it renders a woman infertile remains unclear. The medical treatment of pelvic endometriosis includes hormonal therapy that directly attacks endometriosis lesions or indirectly by inhibiting endometrial proliferation through estrogenic deprivation.

The aim of this study was to compare the efficacy and safety of leuprorelin acetate depot and danazol for endometriosis in infertile women.

Methods: This randomized trial involved 81 women 19-41 years old with regular menses and known pelvic endometriosis who were recruited from the Fertility Center of the Second University of Naples between 1992 and 1999. Fifty-four women were given 3.75 mg of leuprolide acetate depot every 28 days for 24 weeks and the remaining 27 took 200 mg of danazol three times daily for 24 weeks. Efficacy assessments were based on pre-admission and end-of-treatment laparoscopic scores and subjective symptoms scores at 4-week intervals during and after treatment. Safety was evaluated by adverse events and clinical laboratory tests.

Results: In each group, endometriosis growth and symptoms significantly improved during treatment ($p < 0.001$). Significantly fewer patients randomized to leuprorelin acetate (5.5%) withdrew during treatment compared with 18.5% randomized to danazol ($p < 0.05$). After treatment symptoms returned in each group, but severity was less than at admission at all time points ($p < 0.02$). Hypoestrogenic side-effects were more common in those receiving leuprorelin, particularly hot flushes, but anabolic/androgenic side-effects of weight gain and acne were more common in those receiving danazol.

Conclusion: Both leuprorelin acetate depot and danazol are effective in the treatment of endometriosis in infertile patients. The hypoestrogenic side-effects of leuprorelin may be better tolerated than the androgenic, anabolic effects of danazol.

Key words: Endometriosis; Danazol; Leuprorelin acetate depot; Gonadotropin-releasing hormone analogues; Infertility.

Introduction

Endometriosis is one of the commonest benign gynecological conditions with a peak incidence between 30 and 45 years of age and associated with symptoms of cyclical pelvic pain and infertility. The mechanisms that may form the basis for an association between endometriosis and infertility are controversial; the anatomic damage that occurs with severe endometriosis is associated with other mechanisms: increased frequency of ovulation [1]; increased occurrence of hyperprolactinemia; [2] and, increased prostaglandin levels in the peritoneal fluid with possible effects on corpus luteum activity [3, 4]. Despite these uncertainties, clinicians have had to formulate treatment approaches.

There are three main goals in the treatment of endometriosis: pain relief, resolution of endometriotic deposits and restoration of fertility, but there remains a strong bias against medical treatment for endometriosis-associated infertility. A review of the current literature suggests that medical management of endometriosis may be effective in selected patients and in certain settings, including patients undergoing IVF [5].

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Danazol is an isoxazol derivative of 17a-ethinyl-testosterone with multiple and diverse effects on the reproductive system, most of which are mediated through binding either to sex-hormone-binding globulin (SHBG) or to androgen receptors [6]. The main biological property of danazol is suppression of the hypothalamic-pituitary axis via decrease in frequency of gonadotropin releasing hormone (GnRH) pulses and inhibition of the mid-cycle luteinising hormone (LH) surge [7]. The most often seen side-effects are androgenic and anabolic manifestations: weight gain, increased appetite, acne and oily skin. Voice change and hirsutism are rare occurrences and they necessitate immediate cessation of therapy. Hypo-estrogenic manifestations can occur, but are less pronounced than with GnRH analogues.

Leuproreline is a nonapeptide analogue with deletion at position 10 of the aminoacid sequence of the native GnRH hypothalamic decapeptide. Continued exposure of the pituitary gonadotropes to the GnRH analogues results in desensitization of down-regulation with resultant reduction in circulating serum gonadotropin concentrations and inhibition of ovarian steroidogenesis [6, 8, 9]. The most often seen side-effects are hypo-estrogenic manifestations: decreased breast size, hot flushes, irritability and mood changes. Several open randomised or double-blind placebo studies have compared the efficacy of GnRH agonists with danazol [10-18].

This study therefore aimed to assess the efficacy of the depot GnRH-a leuprorelin acetate (Enantone fl. 3.75 mg, Takeda) administered monthly subcutaneously in comparison with danazol (Danatrol cp. 200 mg, Sanofi) orally.

Subjects and Methods

Eighty-one women with laparoscopically confirmed endometriosis who arrived to the Fertility Center of the Second University of Naples between 1992 and 1999 gave their informed consent to be studied. Patients were randomly allocated to 24 weeks of treatment with either 200 mg of danazol capsules by mouth three times a day or 3.7 mg of leuprorelin acetate depot inserted into the subcutaneous tissue every 28 days. Randomization was in the ratio two leuprolide: one danazol.

The median age was 32 years [19-41], with a normal menstrual cycle, median length 30 days [21-42]. The admission procedures included medical history, general physical and pelvic examination, PAP smear, clinical laboratory tests, serum estradiol level (by radioimmunoassay), pregnancy test and laparoscopy. Treatment was begun between days 1 to 7 of the menstrual cycle. Women were given a patient diary record in which to note the date and the duration of any vaginal blood loss, any hot flushes and the date of eventually missed doses. They were seen once a month during the 6-month treatment; at each visit, women had a brief physical exam and were asked about menstruation, symptoms and adverse events. Serum estradiol levels and pregnancy tests were repeated at monthly visits; clinical laboratory tests and pelvic exams every two months; and, a PAP smear and laparoscopy at six months. Post-treatment follow-up visits and all examinations were repeated at 1, 3, 6 and 12 months.

The degree of endometriosis was assessed according to the Revised American Fertility Society (AFS) classification [19]. No more than ten weeks were allowed to elapse between the diagnostic laparoscopy and entry of the patient into the study. Follow-up laparoscopy had to be performed within six weeks of the end of treatment and usually by the same clinician who had performed the original. At each visit, women evaluated symptoms of endometriosis (dysmenorrhea, dyspareunia, pelvic pain not including dysmenorrhea) using a numerical scale (0=none; 1=mild; 2=moderate; 3=severe). At the same time direct questions were asked about vaginal dryness, depression, acne, oily hair or skin, hirsutism, ankle edema, mood swings, headache and voice changes. Changes in libido and breast size were graded as compared with entry: increase [1], no change [2], decrease [3].

Statistical analysis

The one-sided two-sample binomial test was used to evaluate treatment equivalence between leuprorelin acetate depot and danazol with respect to improvement rate of laparoscopic score, AFS stage and total symptom severity score. Leuprorelin acetate was considered clinically equivalent to danazol if the improvement rate of the leuprorelin-treated group was not > 20% lower than that of danazol because this much difference was not considered clinically significant. The two-sample t-test was also used to test for treatment equivalence based on mean reduction in symptom severity score. Other treatment comparisons were two-sided, and all were performed at the 0.05 significance level.

Results

Eighty-one patients were randomized so that two were assigned to receive leuprorelin acetate depot 3.75 mg monthly for every one assigned to receive danazol 200 mg three times a day. Three patients (5.5%) randomized to leuprorelin were withdrawn from the study before completion of the treatment period, compared with five (18.5%) randomized to danazol. Reasons for withdrawal were adverse findings: a greater proportion of patients withdrew on danazol (18.5%) than on leuprorelin therapy (5.5%). Demographic data are summarized in Table 1. There were no statistically significant differences between the treatment groups.

Table 1. — *Demographic data and clinical history of patients enrolled.*

Patient	Leuprorelin acetate depot 3.75 mg monthly (n=54)	Danazol 200 mg three times a day (n=27)	Total (n=81)
Age			
19 to 25	7 (13%)	3 (11.1%)	10 (12.3%)
26 to 30	14 (25.9%)	7 (25.9%)	21 (25.9%)
31 to 35	20 (37%)	11 (40.8%)	31 (38.3%)
36 to 41	13 (24.1%)	6 (22.2%)	19 (23.5%)
Gravidity			
0	49 (90.7%)	25 (92.6%)	74 (91.4%)
1	3 (5.6%)	1 (3.7%)	4 (4.9%)
2 or more	2 (3.7%)	1 (3.7%)	3 (3.7%)
Parity			
0	51 (94.4%)	26 (96.3%)	77 (95.1%)
1 or more	3 (5.6%)	1 (3.7%)	4 (4.9%)
AFS stage at admission			
I (minimal)	20 (37%)	10 (37%)	30 (37%)
II (mild)	14 (25.9%)	7 (25.9%)	21 (25.9%)
III (moderate)	13 (24.1%)	7 (25.9%)	20 (24.7%)
IV (severe)	7 (13%)	3 (11.1%)	10 (12.4%)

Mean total laparoscopy scores decreased from 15.9 ± 1.5 at baseline to 8.6 ± 1.2 at the end of treatment among leuprorelin users and from 16.5 ± 1.9 to 8.5 ± 1.6 among danazol users. The changes were statistically significant ($p < 0.001$) within but not between the treatment groups. Table 2 shows the distribution of patients by AFS stage at baseline and the end of treatment. Complete remission occurred in 21.6% of leuprorelin and 18.2% of danazol recipients. There was no change in laparoscopic score in 5.9% of leuprorelin and 4.5% of danazol users.

Patients were considered symptomatic at entry to the study if they had a pelvic symptoms score of three or more. Seventy-three patients were symptomatic at entry with equal percentage distribution between treatments. Both treatments were associated with a significant reduction in mean total subjective scores but with no difference between the treatments. Total subjective score was the result of pelvic symptoms + physical findings. Although there was a slight increase in total subjective scores during the follow-up post-treatment, the

Table 2. — *Distribution of 73 patients that completed the study by AFS stage at admission and end of 6-month treatment.*

AFS STAGE	Leuprorelin acetate depot 3.75 mg monthly (n=51)	Danazol 200 mg three times a day (n=22)	Total (n=73)
Absent (score=0)			
Baseline	0	0	0
End of treatment	11 (21.6%)	4 (18.2%)	15 (20.5%)
STAGE I (score 1 to 5)			
Baseline	17 (33.3%)	7 (31.8%)	24(32.9%)
End of treatment	25 (49%)	11 (50%)	36 (49.3%)
STAGE II (score 6 to 15)			
Baseline	15 (29.4%)	6 (27.3%)	21 (28.8%)
End of treatment	7 (13.7%)	4 (18.2%)	11 (15.1%)
STAGE III (score 16 to 40)			
Baseline	13 (25.5%)	8 (36.4%)	21 (28.8%)
End of treatment	6 (11.8%)	3 (13.6%)	9 (12.3%)
STAGE IV (score >40)			
Baseline	6 (11.8%)	1 (4.5%)	7 (9.6%)
End of treatment	2 (3.9%)	0	2 (2.7%)

mean scores remained significantly below those at pre-treatment, even at 24 weeks off treatment ($p < 0.02$). Changes of total subjective score during treatment and follow-up are shown in Figure 1. The most common adverse side-effects reported in the study are summarized in Table 3.

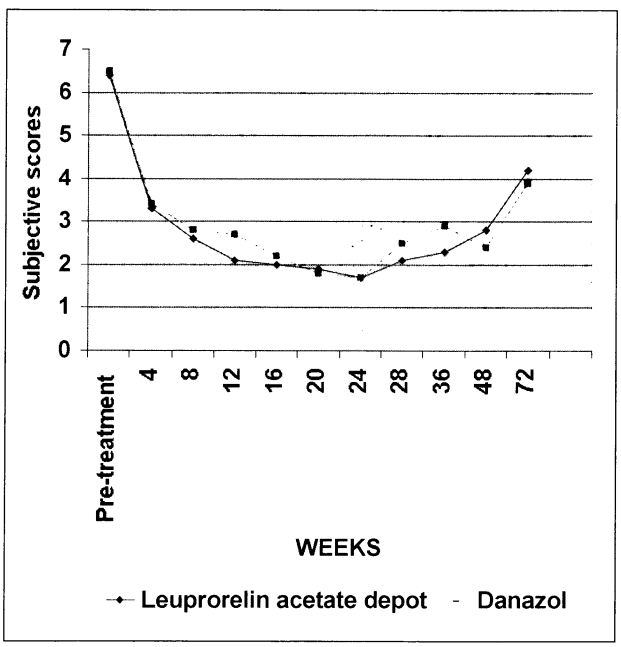

Figure 1. — Changes of total subjective score (pelvic symptoms and physical findings) during treatment and follow-up in symptomatic patients treated with leuprorelin acetate depot (n=51) or danazol (n=22).

Table 3. — *The most common adverse side-effects reported during the study.*

	Leuprorelin acetate depot 3.75 mg monthly (n=54)	Danazol 200 mg three times a day (n=27)
Pain	3 (5.6%)	3 (11.1%)
Headache	3 (5.6%)	1 (3.7%)
Breast pain	3 (5.6%)	0
Nausea	3 (5.6%)	3 (11.1%)
Weight gain	1 (1.8%)	7 (25.9%)
Hot flushes and sweats	52 (96.3%)	16 (59.3%)
Reduction in libido	35 (64.8%)	14 (51.8%)
Acne	20 (37.1%)	15 (55.5%)
Oily hair and skin	14 (25.9%)	14 (51.8%)

Discussion

This study reports the results of a randomized trial of a monthly depot preparation of GnRH agonist leuprorelin acetate compared with oral danazol. Both treatments were shown to be equally effective in inducing resolution of endometriotic deposits and reducing subjective symptom scores.

Our study, in accordance with other trials [16-18], demonstrates that both GnRH analogues and danazol suppress serum estradiol, which is an indicator of ovarian suppression. In general, regression of endometriotic implants is seen inbetween 50 and 90% of patients. As expected, adhesions are not shown to change in most studies, and like with danazol treatment endometriomas larger than 3 cm diameter, although reducing in size on treatment overall, respond poorly and eventually need surgical treatment [6]. However, differences between the two treatments are apparent when side-effects are compared. Danazol has both androgenic and anabolic properties and can induce associated side-effects of weight gain, edema, myalgia, acne, hirsutism and hepatocellular damage [16-18] that are dose related [20]. Two effects of the profound hypo-estrogenemia induced by GnRH agonists are alterations in bone-mineral metabolism and reduction in bone mass [6]. Side-effects associated with GnRH agonists are mainly related to the hypo-estrogenic state and are those generally seen in postmenopausal women, in variable percentages of patients [11-18].

Depending on the needs of the individual patient, the management of infertility may be based on either an expectant strategy or a range of therapeutic options, such as medical treatment, surgery or laparoscopic surgery [21]. Studies in in vitro fertilization have shown that reduced fertilization rates occur in women with endometriosis, particularly those who have ovarian cysts [22]. Besides long-term relief and sustained reduction in symptom severity, the high pregnancy rate in infertility, as well as reattainment of quality of life and well being, favor this therapeutic approach to endometriosis.

Conclusion

Leuprorelin acetate depot and danazol are equally effective in reducing endometriosis growth and symptoms

during treatment and in preventing the return of symptoms during follow-up. Further studies are needed to determine the relative effects of therapies such as leuprorelin acetate depot and danazol in women with infertility caused by endometriosis.

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