FERTILITY AND STERILITY®
VOL. 81, NO. 6, JUNE 2004

Published by Elsevier Inc.
Printed on acid-free paper in U.S.A.

An open and randomized study comparing the efficacy of standard danazol and modified triptorelin regimens for postoperative disease management of moderate to severe endometriosis

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Objective: To compare the efficacy of danazol and triptorelin (Decapeptyl CR, Ferring, Kiel, Germany) in the management of moderate and severe endometriosis in terms of symptom control and revised American Fertility Society (AFS) score reduction, and to evaluate the hormonal profile of patients treated with triptorelin every 6 weeks.

Design: Open and randomized trial.

Setting: Kwong Wah Hospital, a large public hospital in an urban location (Hong Kong).

Patient(s): Forty patients after their first conservative operation for endometriosis, with surgical confirmation of revised AFS stage III or IV endometriosis.

Intervention(s): Postoperative 6 months' therapy of danazol or triptorelin every 6 weeks, postmedical therapy second-look laparoscopy.

Main Outcome Measure(s): Symptom control and patients' tolerance during medical therapy, posttherapy revised AFS score, hormonal profile during triptorelin therapy.

Result(s): Pain control was similar between danazol and triptorelin therapy. There was less breakthrough bleeding with triptorelin. More patients failed to complete the whole course of danazol because of its side effects. The revised AFS score at second-look laparoscopy did not show a significant difference between the two medications. Adequate pituitary suppression was observed with injection of triptorelin every 6 weeks.
Conclusion(s): Lengthening of triptorelin administration intervals from 4 weeks to 6 weeks is effective in maintaining a hypoestrogenic state. Patients were more compliant with triptorelin than danazol. Thus, triptorelin injection every 6 weeks is more cost-effective than conventional regimens. (Fertil Steril® 2004;81: 1522–7. ©2004 by American Society for Reproductive Medicine.)

Key Words: Endometriosis, danazol, triptorelin, symptom control, second-look laparoscopy, pituitary suppression

Endometriosis is a common, benign gynecological disease causing infertility and intolerable symptoms such as dysmenorrhea, dyspareunia, and pelvic pain. Various therapies have been used for treating endometriosis, including surgical and medical strategies. Surgical intervention is the treatment of choice because it has been shown that ablation of the endometriotic lesions increases the pregnancy rate in infertile women (1) and reduces pelvic pain in symptomatic patients (2, 3). However, medical treatment aims to inhibit the growth of endometriotic implants by suppression of ovarian steroids and induction of a hypoestrogenic state and is commonly used as adjuvant treatment after surgery (4).

Danazol, an anti-estrogen, was the first drug approved in the United States for the treatment of endometriosis. The standard dosage is 200–800 mg/d for 6 months. Although danazol has been found to be effective, patients frequently find its side effects to be intolerable. A recent study reported that >50% of the patients taking danazol experienced severe adverse reaction and requested cessation of the therapy (5).

The development of GnRH agonist (GnRH-a) provided an alternative treatment for endometriosis. Gonadotropin-releasing hormone agonist suppresses the release of LH and FSH from the pituitary and results in a hypoestrogenic state that is suitable for the remis-

Received May 28, 2003; revised and accepted December 30, 2003.
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0015-0282/04/$30.00
doi:10.1016/j.fertnstert.2003.12.020

sion of the endometriotic lesions. The side effects of GnRH-a are mainly those of the hypoestrogenic state, similar to those experienced by postmenopausal women. Routine GnRH-a treatment consists of a 6-month course with various choices of formulations, such as nasal spray, daily injection, or monthly depot. Because of the comparative convenience, GnRH-a monthly depots have emerged as the standard choice for the treatment of endometriosis.

There has been consensus that adjunctive medical therapy should be provided after conservative surgical treatment for endometriosis (6). Danazol has been evaluated as a postoperative adjuvant therapy and was found to be effective in reducing pain scores (7–9). Gonadotropin-releasing hormone agonist was also noted to give better outcome, with a longer pain-free period than that of women who were treated with surgery alone (10).

Gonadotropin-releasing hormone agonist depot injection is commonly given on a monthly basis. However, a recent study on the pharmacokinetics and pituitary-suppressive ability of triptorelin (Decapeptyl CR, Ferring, Kiel, Germany) reported on the long-lasting nature of this medication, which could still be detected 2 months after the cessation of the treatment (11). Lengthening the interval between two doses of triptorelin injection can reduce drug dosage, leading to fewer side effects and lower drug cost. Yet this regimen can maintain its effectiveness in the control of the disease.

The present study attempts to compare the efficacy of danazol and every-6-weeks injection of triptorelin in the immediate postoperative management of patients with moderate and severe endometriosis. It also assesses the control of symptoms, patient compliance, side effects, and pelvic peritoneal condition after completion of therapy.

MATERIALS AND METHODS

This open, prospective, and randomized trial was performed at Kwong Wah Hospital, Hong Kong. Ethical approval was obtained for the study from the hospital ethics committee.

During the period of January 1999 to March 2002, we selected patients who were newly diagnosed with and surgically confirmed as having revised American Fertility Society (AFS) stage III and IV endometriosis. They were premenopausal women of age ranging from 18 to 50 years. Patients with recurrent endometriosis; who had previous GnRH-a, danazol, or other ovarian suppression therapies 3 months before the start of the study; and who had known allergic reaction to GnRH-a or danazol were all excluded. Immediately after their first operative resection or ablation of endometriosis implants, they were counseled on the use of postoperative danazol and GnRH-a depot therapy, together with a full explanation of their side effects. The issue of carrying out second-look laparoscopy on completion of therapy was also discussed.

We planned to recruit 40 patients. Almost a hundred patients who satisfied all the inclusion and exclusion criteria had been approached. However, more than half of them declined to participate in the trial. Their reasons were that they did not want to use any adjuvant therapy for fear of the side effects of either medication, they wanted a specific medication and disliked being randomized, they were planning for pregnancy, or finally, but not least, they did not want to undergo another laparoscopy.

For patients who agreed to participate in the trial, an informed consent would be signed, and then they were randomized into two groups: 20 patients in the danazol group and 20 patients in the triptorelin group. A chart was prepared with 40 slots of randomly allocated treatment regime of either danazol or triptorelin, and each patient was assigned to each slot and the corresponding therapy in chronological order. The randomization scheme was generated by using the web site Randomization.com, which is a randomization list generator created at Tufts University according to the published methods (12, 13). The permuted block used in the trial randomization list was 10.

For patients in the danazol group, oral danazol (Danocrine; Sanofi, New York, NY), 600 mg/d (at 200 mg three times daily) was planned to be given continuously for 6 months. Afterward, a second-look laparoscopy would be performed to evaluate the treatment outcomes. The revised AFS endometriosis score would be used for evaluation.

For patients in the triptorelin group, triptorelin (Decapeptyl CR, 3.75 mg depot; Ferring) was planned to be given by intramuscular injection every 6 weeks, and treatment continued for up to four injections. At 6 weeks after the last injection, a second-look laparoscopy would be performed, and the revised AFS score would be used to evaluate the treatment outcomes. To investigate the suppressive capacity after lengthening of the interval between each triptorelin injection, hormonal tests (FSH, LH, and E_2) were checked before treatment, just before the second injection and at 6 weeks after the last injection. Moreover, a luteinizing hormone–releasing hormone (LHRH) stimulation test (100 μg of LHRH is injected IV, and the plasma concentrations of FSH and LH are recorded at 15, 30, and 60 minutes after the LHRH challenge) was carried out at 6 weeks after the last injection.

During the study period, all patients were followed up at 6-week intervals to check for symptom control (pain score and urinary and bowel symptoms score), breakthrough bleeding, and side effects of the medication. Pain score was contributed to by patients' self-assessment of their severity of dysmenorrhea and pelvic pain since their last visit. Each patient was interviewed by the investigator in person, and the guideline for grading was *no pain*, meaning a completely pain-free status; *mild pain*, for pain that did not cause concern to the patient and did not require analgesics; *moderate pain* for pain that bothered the patient or required therapy for

pain relief; and *severe pain*, for significant pain leading to avoidance of daily work and activities or regular use of strong analgesics. No dysmenorrhea and mild, moderate, and severe dysmenorrhea were scored as 0, 1, 2, and 3, respectively. No pelvic pain and mild, moderate, and severe pelvic pain were scored as 0, 1, 2, and 3, respectively (14, 15), making up a maximum pain score of 6.

Similarly, urinary symptoms and bowel symptoms were each scored from 0 to 3, giving a maximum score of 6. Breakthrough bleeding was also scored from 0 to 3. The same applied to the assessment of each complaint of side effects. If symptom control was unsatisfactory or side effects became significant, the patient could choose to terminate the medication or switch to another therapy. The final follow-up was scheduled for 12 weeks after laparoscopy, to check for recurrence of symptoms after completing the therapy and to check for return of the menstrual period.

Patients' demographic data, their pain and the various symptom scores, and the revised AFS endometriosis score were analyzed by Student's *t*-test. Patients' compliance in completing therapy was compared by the χ^2 test. For all analyses, $P<.05$ was considered statistically significant.

RESULTS

At visit 1 (recruitment visit), 20 patients were enrolled into the danazol group and another 20 patients into the triptorelin group. For the danazol group, the mean age was 36.9 ± 5.6 years, mean body mass index (BMI) was 23.1 ± 3.9 kg/m^2 (range, 17.8–29.6 kg/m^2), mean gravity was 1.4 ± 1.2, and mean parity was 0.6 ± 0.9. For the triptorelin group, the mean age was 36.7 ± 6.9 years, mean BMI was 24.2 ± 4.0 kg/m^2 (range, 17.8–33.0 kg/m^2), mean gravity was 1.3 ± 1.3, and mean parity was 1.0 ± 0.9. All demographic data showed no significant difference between the two groups (Table 1). On further analysis of BMI, a similar distribution of the various subgroups was noted between the two study groups: 15% were underweight, 45%–55% were of normal build, and 30%–40% were considered to be obese.

The mean revised AFS score at the initial operation before medical therapy was 53.6 ± 32.1 in the danazol group and 59.9 ± 31.1 in the triptorelin group, also with no significant difference. Pain was the commonest presenting feature in both stages III and IV endometriosis. Some patients presented with an incidental ultrasound finding of one or more ovarian cysts. One patient had stage IV endometriosis but minimal dysmenorrhea, presented during investigation for primary subfertility (Table 1). The preoperative symptoms assessment in the danazol group revealed a mean pain score of 2.20 ± 1.28 and a mean urinary and bowel symptoms score of 0.40 ± 0.88, whereas these were 2.80 ± 1.36 and 0.20 ± 0.52, respectively, in the triptorelin group. All data showed no significant difference (Table 2).

The majority of the patients had excision of one or more endometriotic cysts, with a fairly even share of unilateral and bilateral ovarian cystectomy in either group. One patient in the danazol group had unilateral oophorectomy, whereas one patient in the triptorelin group had unilateral oophorectomy together with contralateral ovarian cystectomy (Table 1).

TABLE 1

Demographic and baseline data of the patients.

Parameter	Danazol group (n = 20)	Triptorelin group (n = 20)
Mean age	36.9 ± 5.6	36.7 ± 6.9
Mean gravity	1.4 ± 1.2	1.3 ± 1.3
Mean parity	0.6 ± 0.9	1.0 ± 0.9
Mean height (m)	1.57 ± 0.06	1.57 ± 0.04
Mean weight (kg)	57.2 ± 10.0	59.3 ± 10.1
Mean BMI (kg/m^2)	23.1 ± 3.9	24.2 ± 4.0
No. of patients with BMI <19	3	3
No. of patients with BMI 19 to <25	11	9
No. of patients with BMI 25 to <30	6	7
No. of patients with BMI ≥30	0	1
Mean pretherapy revised AFS score	53.6 ± 32.1	59.9 ± 31.1
No. of patients with stage III disease	11	8
Presenting features		
Increasing dysmenorrhea	5	5
Acute abdominal pain	3	0
Chronic pelvic pain	0	1
Incidental ultrasound finding	3	2
No. of patients with stage IV disease	9	12
Presenting features		
Increasing dysmenorrhea	3	6
Acute abdominal pain	1	3
Incidental ultrasound finding	4	3
Subfertility	1	0
Operation performed		
Unilateral ovarian cystectomy	13	15
Bilateral ovarian cystectomy	6	4
Unilateral oophorectomy	1	0
Unilateral oophorectomy + contralateral ovarian cystectomy	0	1

Note: Values are mean ± SD. *P* values by Student's *t*-test comparing mean values between study groups were all not statistically significant.

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At visit 2, after the first 6 weeks of therapy, the mean pain score dropped to 0.74 ± 1.05 in the danazol group, whereas in the triptorelin group, it was 0.85 ± 0.99. There was no statistically significant difference between the two groups, but there was significant reduction of pain score when compared with that before therapy in both groups ($P<.001$ in both groups). The mean urinary and bowel symptoms score was 0.21 ± 0.54 in the danazol group and was 0 in the triptorelin group, with no significant difference between the two groups, and also no difference when compared with that before therapy. The breakthrough-bleeding score was 1.05 ± 0.80 in the danazol group and 1.10 ± 0.91 in the triptorelin group, with no significant difference (Table 2). The FSH, LH, and E_2 levels were well suppressed in all patients in the triptorelin group.

TABLE 2

Symptoms score at various visits.

Visit	Danazol group	Triptorelin group	*P* values
Visit 1 (0 wk)			
n	20	20	
Mean pain score	2.20 ± 1.28	2.80 ± 1.36	NS
Mean urinary/bowel score	0.40 ± 0.88	0.20 ± 0.52	NS
Visit 2 (6 wk)			
n	19	19	
Mean pain score	0.74 ± 1.05	0.85 ± 0.99	NS
Mean urinary/bowel score	0.21 ± 0.54	0	NS
Breakthrough bleeding score	1.05 ± 0.80	1.10 ± 0.91	NS
Visit 3 (12 wk)			
n	17	19	
Mean pain score	0.47 ± 0.87	0.53 ± 0.84	NS
Mean urinary/bowel score	0.12 ± 0.49	0	NS
Breakthrough bleeding score	0.59 ± 0.80	0.05 ± 0.23	<.02
Visit 4 (18 wk)			
n	14	19	
Mean pain score	0.21 ± 0.58	0.26 ± 0.56	NS
Mean urinary/bowel score	0	0.05 ± 0.23	NS
Breakthrough bleeding score	0.29 ± 0.47	0	<.05
Visit 5 (24 wk)			
n	12	18	
Mean pain score	0.17 ± 0.58	0.28 ± 0.67	NS
Mean urinary/bowel score	0.17 ± 0.39	0	NS
Breakthrough bleeding score	0.25 ± 0.45	0.06 ± 0.24	NS
Visit 6 (36 wk)			
n	12	18	
Mean pain score	0.50 ± 0.80	0.61 ± 0.78	NS
Mean urinary/bowel score	0.17 ± 0.58	0.06 ± 0.24	NS
Breakthrough bleeding score	0.08 ± 0.29	0.06 ± 0.24	NS

Note: Values are mean ± SD. NS = not significant.
*By Student's *t*-test comparing means for the two study groups.

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TABLE 3

Patients completing therapy.

Condition	Danazol group	Triptorelin group
Patients unable to complete therapy	7	1
Patients completed whole course of therapy	13	18[a]

[a] $P<.05$ by χ^2 for the two study groups.

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At all subsequent visits, the pain score remained low with no significant difference between the two groups. There was also no difference in the urinary and bowel score. The breakthrough-bleeding score was significantly lower in the triptorelin group at visit 3 and visit 4 (Table 2).

At visit 5 (24 weeks), the FSH, LH, and E_2 levels were all well suppressed in all patients in the triptorelin group. The LHRH stimulation test showed no increase in LH level in all patients, but there was an increase in FSH level in only one patient.

There were nine patients who had their therapy terminated during the study (seven in the danazol group and two in the triptorelin group). At visit 2 (6 weeks), one patient in the danazol group stopped the medication herself within 2 weeks after therapy, complaining of severe fluid retention. Another two patients requested to stop the therapy. One complained of severe shivering, and the other developed hot flushes and sore throat. One patient in the triptorelin group was excluded from the study because she started taking combined oral contraceptive pills at the same time. However, she wanted to continue with triptorelin and agreed to stop the pills.

At visit 3 (12 weeks), one patient in the danazol group requested to stop the therapy because of severe sore throat. Another two patients requested to change their therapy to triptorelin because of significant breakthrough bleeding. At visit 4 (18 weeks), one patient in the danazol group requested to switch to triptorelin because of hoarseness of voice. One patient in the triptorelin group requested to stop the therapy because of developing an irritable mood.

Altogether, 13 patients in the danazol group completed their 6 months' therapy. Only 12 underwent second-look laparoscopy because 1 patient refused to have laparoscopy on completion of her treatment. In the triptorelin group, only one patient failed to complete the 6 months of therapy. In addition to the patient who was excluded from the study at visit 2 (because of simultaneous intake of oral contraceptive pills), 18 patients were scheduled for second-look laparoscopy. Unfortunately, one patient was suspected to have bronchial aspiration during anesthesia, and the laparoscopy was abandoned, leaving 17 patients for evaluation. The mean revised AFS score in the danazol group was 23.6 ± 28.4, and it was 34.8 ± 25.6 in the triptorelin group. There was no significant difference between the two groups. However, there was a statistically significant higher rate of completion of 6 months' therapy in the triptorelin group than in the danazol group ($P<.05$; Table 3).

At visit 6 (36 weeks; i.e., 12 weeks after stopping danazol or 18 weeks after the last injection of triptorelin), 11 of the 12 patients in the danazol group found their periods returned, whereas only 4 of the 18 patients in the triptorelin group had menstruation. The difference was statistically significant ($P<.01$).

The commonest side effects in the danazol group were weight gain (12 patients) and acne (9 patients), followed by hoarseness of voice, sore throat, and fluid retention. One patient complained of joint pain. Another patient stopped the therapy herself because of developing "shivering" after beginning danazol. The increase in weight was generally stated to be around 2 to 5 kg, except in one patient, who assessed the increase to be 10 kg. Acne was either of mild or moderate

TABLE 4

Summary of common side effects throughout the course of therapy.

Visit no.	Danazol group (mean scores)			Triptorelin group (mean scores)		
	Weight gain	Acne	Throat/voice problem	Vasomotor symptoms	Mood problem	Joint pain
2	0.30	0.25	0.15	0.70	0.15	0
3	0.53	0.41	0.18	0.74	0.58	0.26
4	0.64	0.57	0.14	0.79	0.79	0.16
5	0.50	0.33	0.25	0.94	0.67	0.06
6	0	0.08	0.08	0.50	0.33	0.11

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severity. However, no patient wanted to stop the therapy because of weight gain or acne. Both these problems also subsided on stopping danazol.

Two patients developed sore throat and stopped the therapy because of fear of further progression, to hoarseness of voice. One patient suffered from hoarseness of voice after 18 weeks of danazol and needed to switch to triptorelin. Another two patients developed hoarseness of voice by the end of 6 months of danazol therapy. Two patients experienced severe fluid retention. One of them requested termination of therapy, whereas the other continued danazol therapy after a short course of diuretics.

In the triptorelin group, the most frequent complaint was vasomotor symptoms (hot flushes and sweating; 15 patients), followed by mood disturbance (9 patients), mainly in the form of irritable feeling, insomnia, and nightmare. Three patients complained of bone pain. One had decreased libido. The vasomotor discomfort was already obvious after the first injection. It had a cumulative effect, with progressive increase in the severity at successive visits, and the maximum score was noted at the visit after the last injection. However, all patients found this side effect to be tolerable. Mood changes only started to be obvious after the second injection. Mood changes also showed a cumulative effect, and one patient requested to terminate her therapy (after three injections) because of severe irritability (Table 4).

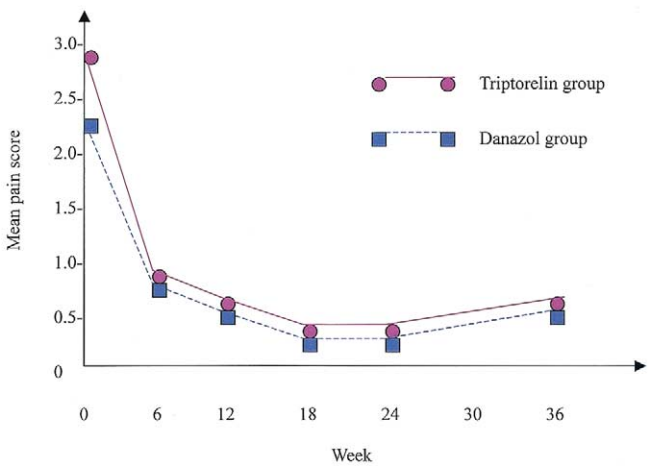
DISCUSSION

After conservative surgery for stage III and IV endometriosis, both danazol and triptorelin were equally effective in the control of pain, as shown by the significant reduction of pain score at visit 2 compared with the pain score before therapy. For both regimens, the effect of pain relief could last to the last visit, that is, 12 weeks after completion of therapy. The change in pain scores over time throughout each visit is illustrated in Figure 1. Complaints about bowel and urinary symptoms were relatively uncommon in both study groups. The higher rate of completion of every-6-weeks triptorelin therapy reflected better compliance than that for danazol in the long run. This was the result of higher incidence of breakthrough bleeding with danazol, of difference in the tolerance for the various side effects of the two therapies, and probably of the more convenient administration of triptorelin (four injections in total, compared with the three times per day oral intake of danazol).

Persistent breakthrough bleeding not only causes inconvenience to the patient but also poses the worry of ineffectiveness of the therapy in creating a pseudomenopausal status. The significantly higher rate of breakthrough bleeding after danazol and subsequently, the need to switch to triptorelin illustrated the importance of starting the treatment with a medication that was effective in maintaining absolute amenorrhea. Moreover, significantly fewer patients on triptorelin had return of their period, and together with the very low breakthrough-bleeding rate at the final visit, this further

FIGURE 1

Changes in pain scores over time throughout each visit. The maximum pain score was 6.



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illustrated the power of triptorelin to maintain the hypoestrogenic status.

Weight gain and acne were common side effects of danazol; so were vasomotor symptoms and mood changes with triptorelin. Most patients showed good tolerance to these problems, except one patient in the triptorelin group who stopped the therapy because of severe irritable mood. Acceptance of these well-known side effects can be accounted for by the adequate explanation that was given to each patient before therapy was started and by the fact that the patients understood that these effects were reversible.

However, regarding the effect of hoarseness of voice after danazol, the possibility of irreversible change created fear about continuing with the therapy once some problems with the throat or voice arise, leading to termination of therapy in two patients who complained of sore throat. Three patients did develop hoarseness of voice after danazol, and its permanent effect was observed on subsequent follow-up. Fluid retention might be relieved with the use of a short course of diuretics. One patient stopped the danazol therapy because of some unusual side effects, namely shivering. This might reflect her unwillingness to continue with the therapy rather than a genuine side effect of the medication.

Successful suppression of FSH, LH, and E_2 levels confirmed that the effectiveness of the triptorelin was maintained when the interval between injections was lengthened from the usual 4 weeks to 6 weeks. This finding was also reported by Tse et al. (16) in 2000, who showed that an every-6-weeks dosing regimen of triptorelin depot resulted in a consistent hypoestrogenized state, which was similar to that achieved by the conventional regimen.

In addition, we found that this was not related to the build of the patient, because successful suppression together with symptoms control and amenorrhea were noticed in both lean and obese patients. Among the eight patients in the triptorelin group with BMI of $\geq$25 kg/m^2, apart from the one who was excluded from the study at visit 2 (because of concomitant taking of oral contraceptive pills), they all demonstrated adequate control with the extended interval-triptorelin dosing. Even the patient with a BMI of 33.0 showed no elevation of FSH and LH level on LHRH stimulation test. Six of these seven patients did not have return of their period at the last visit (at 18 weeks after the last injection).

By giving the injections at 6-week intervals, the total dose of medication can be reduced, thus lowering the total cost of the therapy and theoretically minimizing the side effects, all of which can improve drug compliance. The results obtained at second-look laparoscopy further reassured that treatment with triptorelin every 6 weeks is comparable to treatment with the standard danazol regimen.

Thus, injection of triptorelin every 6 weeks after conservative surgery for stage III and IV endometriosis was more cost-effective than the danazol regimen in terms of patients' acceptance, compliance, symptom control, maintenance of hypoestrogenic status and pituitary suppression, and post-therapy pelvic condition.

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