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Effects of triptorelin versus placebo on the symptoms of endometriosis

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Objective: To compare the effect of a GnRH-agonist, triptorelin, versus placebo on the symptoms of endometriosis.

Design: A prospective, randomized, double-blind study of 6 months of treatment followed by 12 months of follow-up.

Setting: Departments of Obstetrics and Gynecology at two universities and one general hospital.

Patient(s): Forty-nine women with symptoms of laparoscopically verified endometriosis.

Intervention(s): Triptorelin depot or placebo was given every 4 weeks. Clinical evaluation, including the Duration Intensity Behavior Scale and Visual Analogue Scale for pain, was performed before the injections and up to 12 months after treatment. A control laparoscopy was performed 4–6 weeks after the last injection.

Main Outcome Measure(s): Quantitation of pain.

Result(s): Twenty-four patients had active treatment and 25 received placebo. Pain symptoms according to both scales were significantly more reduced after 2 months of triptorelin treatment compared to placebo. The extent of endometriotic lesions was reduced 50% during triptorelin treatment and increased 17% during placebo. The average area of endometriotic lesions was reduced 45% during triptorelin treatment but was unchanged during placebo. Side effects, mainly hot flushes, were experienced by 80% of the actively treated group but also by 33% of patients in the placebo group. Because of recurrent symptoms, only five patients could be observed for 12 months after completion of treatment.

Conclusion(s): Triptorelin reduces endometriotic lesions and pain to a significantly higher degree than placebo. (Fertil Steril® 1998;69:702–8. ©1998 by American Society for Reproductive Medicine.)

Key Words: Endometriosis, GnRH-agonists, triptorelin, placebo, pain scoring, long-term follow-up, Duration Intensity Behavior Scale, Visual Analogue Scale

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Endometriosis is considered to be an estrogen-dependent disease. A variety of hormonal treatments for endometriosis have been used, including drugs such as danazol, progestogens, gestrinone, gossypol, clomiphene citrate, tamoxifen, prostaglandin synthetase inhibitors, and GnRH analogues. Most of the clinical documentation of the effect of GnRH analogues in the treatment of endometriosis comes from comparative studies with danazol (1, 2).

Few studies have investigated the effect of GnRH analogues in comparison with placebo (3–5). However, the effect of a gestagen versus placebo or versus observation has been compared in double-blind randomized studies (4, 6–8). Furthermore, long-term follow-up data on GnRH agonist treatment of endometriosis symptoms are scarce (9, 10).

Triptorelin differs from GnRH in position 6 of the molecule where glycine is replaced by D-tryptophan. As a result, triptorelin has a much higher receptor affinity, a 100-fold higher activity, and a considerably longer plasma half-life than GnRH (11, 12). In a sustained-release preparation, triptorelin (Decapeptyl Depot) has been enclosed in biodegradable polymer particles of DL-lactide-coglycolide from which it is released at concentrations high enough to suppress ovarian function for 1 month.

The most common symptoms of endometriosis are severe pelvic pain and dysmenorrhea.

A placebo-controlled study of the effect of hormonal treatment on pain associated with endometriosis is lacking. Useful instruments for quantitation of pain have now become available (13, 14). Upon first injection of triptorelin, as with other GnRH-agonists, there is a transient increase of LH and FSH with a concomitant increase in the production of ovarian steroids (15). This transient increase has transiently increased the severity of symptoms related to endometriosis, such as pain in some cases. After this initial stimulation, the release of gonadotropins is inhibited, and the castration level of estrogen is achieved after 2 to 4 weeks.

The aim of this prospective, randomized, double-blind study was to determine the effect of monthly injections (for a total of 6 months) of sustained-release triptorelin compared with placebo on pain related to endometriosis. The effect on the clinical symptoms associated with endometriosis was observed for another 12 months after the cessation of treatment. The efficacy of triptorelin and placebo, respectively, in reducing the number and size of endometriotic lesions was determined.

MATERIALS AND METHODS

A total of 49 women aged 19–44 years (mean age, 31 years) were included in this placebo-controlled, double-blind, parallel study. Three centers participated with separate randomization. All women had given written consent, the study was approved by the local ethics committees, and the guidelines from the Helsinki Declaration of 1975 on human experimentation were followed.

All the women had been menstruating regularly (25–35 day intervals) for at least 3 months before the study, and all had clinical symptoms of endometriosis. The initial diagnosis of endometriosis had been made within 1 year of entering the study for 34 women (69%). Only one patient in the triptorelin group and three patients in the placebo group had had endometriosis for more than 5 years. Four patients in the triptorelin group and eight patients in the placebo group had been treated for endometriosis before the study (danazol, progestins, oral contraceptives, nafarelin, or buserelin).

No patient had taken oral contraceptives or any other oral steroid therapy for at least 3 months preceding the study, nor had they taken long-acting depot gestagens or GnRH-agonists within the preceding 6 months. None of the women had been breast-feeding or pregnant within the preceding 3 months or had a history of osteoporosis or coagulation disorders. The treatment groups were comparable with regard to different background variables such as age, body weight, vital signs, and menstrual pattern and pregnancies as well as with regard to medical history and pain data.

At the pretreatment descriptive laparoscopy, which was performed for clinical reasons, implants and adhesions were scored according to RAFS (the revised American Fertility Society scoring) criteria (16). Patients with intraperitoneal adhesions that made visual inspection and careful evaluation of the extension of the endometriotic lesions difficult or impossible were excluded from the study. The endometriotic surface area was measured at the end of the operation with the assistance of a graded probe and the number of endometriotic lesions was assessed. In all cases but two the diagnosis was quite obvious visually and no histologic examination was done to confirm the diagnosis.

Only one patient with RAFS stage IV was included in the triptorelin group; all the others had mild to moderate endometriosis. The women were randomized to receive 3.75 mg of triptorelin (n = 24) (Decapeptyl Depot) or placebo (n = 25). One patient in the placebo group became pregnant before treatment was started and was therefore excluded from the study. The drug preparations were kept in kits of identical appearance and injected IM every 28 days for a period of 24 weeks. The first injection was given at the second visit, one of the first 4 cycle days within 1 month after the initial laparoscopy. All patients received their injections at the clinic.

The patients, who were asked to use barrier contraception during the study period, were seen at the clinic by the investigating physician at the first laparoscopy and after 1, 3, and 5 months of treatment and at the control laparoscopy, which was performed 4–6 weeks after the final injection. After 2, 4, and 6 months of treatment, the patients were monitored by a study nurse. At all visits an evaluation of signs and symptoms as well as patient evaluation of pain, dyspareunia, bleeding, and use of analgesics was performed. Blood samples were drawn just before the first injection and thereafter at monthly intervals for laboratory studies including determination of serum concentrations of E_2. A pelvic examination was performed at each visit to the doctor. During the entire study period, the patients kept a diary to document bleeding, consumption of analgesics, and adverse effects.

The efficacy of the treatment was evaluated according to changes in symptoms, visible endometriosis extension, and frequency and amount of bleeding. From the start of the treatment to the end of the trial, pain was charted for five different parameters and was assessed at every visit by the Duration Intensity Behavior Scale (DIBS; 13, 14), by the Visual Analogue Scale (VAS; 17), and by direct questions about pelvic pain, dysmenorrhea, and dyspareunia.

The DIBS was expressed in seven stages: 0 = no pain; 1 = some pain which you easily can disregard; 2 = some pain which you cannot disregard but which does not make your usual activities more difficult; 3 = pain that makes concentration on more demanding tasks more difficult; 4 = pain that makes most things you do more difficult except the most basic; 5 = pain that is so severe that you have to rest; 6 = pain that is so severe that you cannot stand it. The two ends of the VAS represented no pain and unbearable pain, respectively. The degree of dysmenorrhea, dyspareunia, and

pelvic pain was also scored separately into four degrees: none, mild, moderate, and severe. The bleeding pattern and the consumption of analgesics were recorded in the patients' diaries.

All patients who completed the 6 months of treatment were seen by the investigating physician every third month for a follow-up period of 12 months for a checkup identical to those performed during treatment. A recurrence was defined as the first time a patient experienced DIBS-rated pain that was at least as severe as before therapy.

Statistical Methods

Two-way analysis of variance (ANOVA) with repeated measures on one factor was used for the analysis of DIBS, VAS, pelvic pain, dysmenorrhea, and dyspareunia. Residual analysis was used to check for the adequacy of the model. For within-group analyses, ANOVA (repeated measures) was used. Results were also confirmed by nonparametric analyses when divergence from normality appeared. The median test was used for the analysis of the difference between groups or implants. The same test was used for the analysis of endometriotic tissue data.

RESULTS

One patient dropped out of the study after one triptorelin injection because of hypoestrogenic side effects and marked depression. Two patients dropped out from the placebo group, one before the first injection because of pregnancy and one after 4 months because of insufficient effect. The mean estradiol concentration in serum decreased in the women given triptorelin, from a mean of 326 pmol/L (SD 274) before treatment to 111 pmol/L (SD 79) after 2 months. Consistent concentrations below 180 pmol/L, regarded as castration level in the laboratory used, were thereafter achieved in all patients but one during the treatment period. In the placebo group, the mean serum estradiol level was unchanged during the study period. There were no significant differences in hematology, blood chemistry, and urinary analyses in the two groups during the study.

The total pain score was significantly reduced in the triptorelin group in relation to the pretreatment value after 2 months in comparison to placebo ($P < 0.01$). The estimate of the mean difference of pain score between the baseline and 6 months of triptorelin treatment was 2.85 (95%, CI 2.2–3.5), which is both statistically and clinically significant. The mean DIBS was the same before the first injection in both groups but fell to less than one in the triptorelin group within 3 months and was sustained at that level throughout the treatment period. In the placebo group, the DIBS points were not affected significantly (Fig. 1A).

The scores obtained by VAS decreased during the triptorelin treatment to a sustained level lower than one point after 3 months, and after 6 months the mean was 3.5 (CI 2.58–4.44). In the placebo group the median values decreased 35% during the study period (Fig. 1B). On the basis of detailed questions, pelvic pain was reduced during treatment with triptorelin but there was no change in the amount of pelvic pain in placebo group (Fig. 1C).

Before treatment, 13 patients actively treated and 20 treated with placebo complained of dyspareunia. The frequency was reduced during the treatment period, and after 6 months the 3 patients in the triptorelin group (13%) and 11 in the placebo group (48%) had dyspareunia. Defecation pain and bowel pressure were reported before treatment by six patients in the triptorelin group and five in the placebo group. The problem disappeared in all but one in the triptorelin group but remained unchanged in the placebo group.

Before treatment, pelvic tenderness was found in 20 women in the triptorelin group and in 23 in the placebo group. It was mild or moderate in 18 and 19 cases, respectively, and the distribution of intensity was similar in the two treatment groups. At the end of the 6-month treatment period, pelvic tenderness was found in 4 women in the triptorelin group and in 19 women in the placebo group.

The mean total RAFS scores at inclusion were 7.7 in the triptorelin group and 7.2 in the placebo group. The number of patients in the different AFS stages in the two groups were distributed as follows for stage I–IV: for triptorelin, 14, 8, 1, 1 and for the placebo group, 11, 12, 2, 0. Control laparoscopy was performed in 46 patients, 23 in each group. In the triptorelin group the lesions disappeared in four patients from a maximal score of four and progress was seen in three patients. In the placebo group, the lesions disappeared in only one patient with a score of four. There was progress in 12 patients, but the mean score increased only to 7.7.

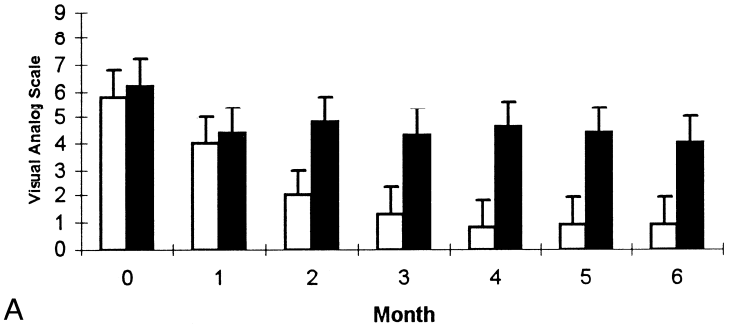
The average area of endometriotic lesions decreased by 45% during treatment with triptorelin, whereas it remained unchanged in the placebo group. Neither triptorelin nor placebo had any effect on the number of implants. The adhesion score was reduced in the triptorelin group from 19 to 9 but was unchanged in the placebo group.

All women were regularly menstruating at inclusion, although six of them had a minor variability (4–7 days). Within 2 months, no woman in the triptorelin group was menstruating and after 4 months no woman reported spotting. In addition, in the placebo group, at least seven women missed one menstrual cycle and four women missed two menstrual bleeds, although not consecutively, during the treatment period. Triptorelin eliminated dysmenorrhea, whereas placebo had no effect on that condition.

Most adverse reactions appeared during the first month of treatment. The intensity was moderate to severe in most of the cases. After 1 month of treatment the number of women in the triptorelin group who complained of hot flushes had increased from 2 to 14 and did not increase significantly thereafter. In the placebo group, the number increased from six to nine and remained unchanged thereafter. The number

FIGURE 1

(**A**), The mean endometriotic pain score according to the Visual Analog Scale (0–10 points) before and during treatment with triptorelin compared with placebo. Triptorelin = *open bars*; placebo = *solid bars*. (**B**), The mean endometriotic pain score according to the Duration Intensity Behavior Scale (0–6 points) before and during treatment with triptorelin compared with placebo. Triptorelin = *open bars*; placebo = *solid bars*. (**C**), The mean endometriotic pain score (0–3 points) according to a questionnaire concerning pain before and during treatment with triptorelin compared with placebo. Triptorelin = *open bars*; placebo = *solid bars*.



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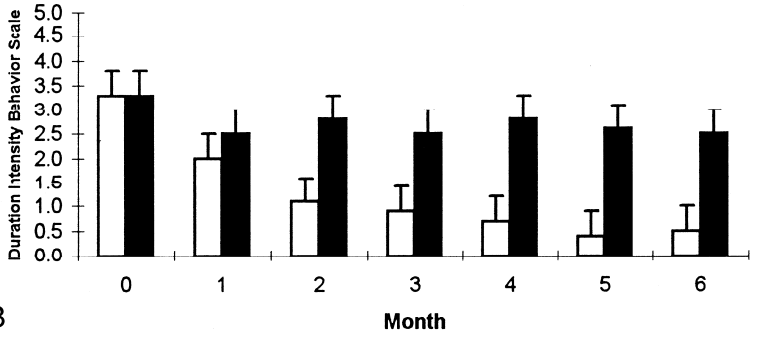

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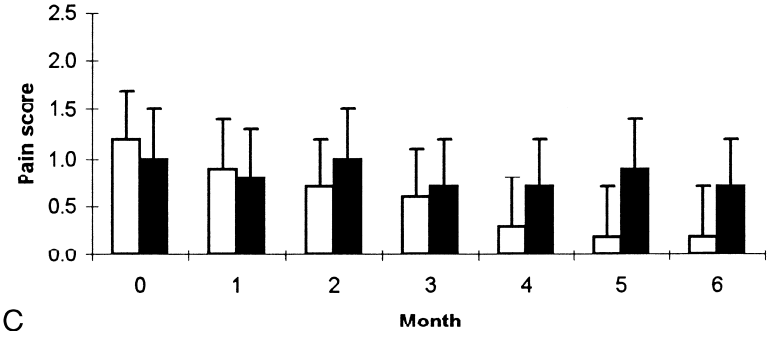

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TABLE 1

Reasons for dropping out of a 12-month follow-up period after 6 months of treatment with triptorelin or placebo.

Therapy	Reason for dropping out			
	Insufficient efficacy	Other reason	Pregnancy	Completed
Triptorelin (n = 23)	4z	9	5	5
Placebo (n = 23)	16	1	3	3

of women complaining of night sweats followed the same pattern.

Sleeping disturbances were reported by 9 women in each group before treatment and increased only in the actively treated group to 20 after 2 months of treatment. Problems with decreased libido became more common in the triptorelin group but declined in the placebo group. No major side effects (e.g., dizziness, nausea, vaginal dryness, urinary tract symptoms, upper respiratory symptoms, arthralgia, or fatigue) of triptorelin or placebo were reported. At the end of the treatment period, some symptoms were reported by 70%–80% of the actively treated patients and by 30%–40% in the placebo group.

During follow-up, the drop-out rate was lower in the triptorelin group than in the placebo group. Thus, triptorelin-treated patients dropped out after a median participation time of 9 months, whereas the placebo patients dropped out after 6 months. Eleven triptorelin patients were in the study for at least 1 year. Only eight patients altogether completed the total trial period of 18 months, five in the triptorelin group and three in the placebo group (Table 1). One woman in the triptorelin group moved from Sweden soon after completing therapy and was lost to follow-up.

Other reasons for dropping out of the triptorelin group during the follow-up period were increasing pain leading to further hormonal treatment (n = 4), pregnancy (n = 5; after 6, 6, 6, 9, and 12 months), initiation of infertility treatment (n = 2), starting contraceptive pills (n = 5), and reversible weight loss resulting in treatment at the internal medicine clinic (n = 1). Most of the patients randomized to placebo (n = 16) dropped out because of insufficient efficacy at 6 months. Nine patients insisted on obtaining hormonal therapy for endometriosis soon after the control laparoscopy, and in one case diathermy of residual endometriosis lesions was performed at the control laparoscopy. Three women became pregnant (after 9, 9, and 12 months, respectively), and one was lost to follow-up.

Six of the 11 patients in the triptorelin group who remained in the trial after 6 months of follow-up had less pain than before therapy. Four of them had recurrent pain. Four of the five patients observed for 12 months after triptorelin therapy had less pain than before treatment. In the placebo group, the pain scores increased insignificantly during follow-up but did not reach the same level as before treatment.

Dysmenorrhea, which had been eliminated during triptorelin therapy, returned in all triptorelin patients but one during follow-up. Triptorelin had reduced dyspareunia during therapy, and during follow-up the score remained low. Three months after therapy, all triptorelin patients had resumed vaginal bleeding except one, who commenced bleeding after 12 months.

Some of the side effects reported during the treatment remained after treatment. Hot flushes were reported by two patients in the triptorelin group 3 months after completion of treatment. In the placebo group one patient reported hot flushes during the whole follow-up period. Night sweats were reported in two patients 3 months after completing triptorelin treatment and in one patient 6 months after completing active treatment and also in one patient in the placebo group 3 months after completing treatment.

There was no difference in the frequency of sleeping problems, headache, or fatigue between the groups. Dizziness was reported in four patients in the triptorelin group 9 months after treatment. One patient was dizzy until month 12, another until month 15. No dizziness was reported in the placebo group. Fatigue was reported in the triptorelin group by three of the patients, after 9 and 12 months, respectively, and by two patients after 15 months. Fatigue was reported by three patients in the placebo group after 9 and 12 months, respectively.

DISCUSSION

This placebo-controlled, double-blind study showed that triptorelin was highly effective compared to placebo in treating pain symptoms associated with endometriosis. In fact, after 2–3 months of treatment, the pain was eliminated in most patients.

This study showed that the effect of triptorelin on the number of endometriotic lesions is not significant compared to placebo. The control laparoscopy was performed 4–6 weeks after the last injection to evaluate the effect on the lesions of ovarian down-regulation for 6 months. Some authorities have recommended a control laparoscopy 3 months after the end of treatment to determine if there is a permanent effect on the lesions (i.e., that the lesions are not invisible because of hypoestrogenism). However, it is well known that endometriotic lesions may be reactivated or recur at any time after the end of a hypoestrogenic treatment, and there is no specific time period following treatment after which it can be determined whether the disease has been cured (18, 19). However, the effect on pain symptoms was significantly better during treatment with triptorelin than with placebo.

The signs and symptoms of endometriosis vary, partially depending on where the endometrial tissue implants are located. Patients with severe symptoms do not always have widespread lesions. The results of this study confirm previous data in finding that there is no correlation between the extension of endometriotic lesions and pain symptoms. This observation implicates other factors such as inflammatory processes in the cause of pain. As endometriosis is a chronic disease, the effect on clinical symptoms is the most important. Lesions infrequently progress to create severe organic changes. After the end of treatment, pain often recurs within a few months, which is why some kind of treatment to prevent recurrence should be recommended for women who do not want to become pregnant.

There was a low rate of breakthrough bleeding in this study, which compares favorably with results obtained with leuprolide acetate where spotting was reported on at least one occasion in 17 of 27 treated patients (3). The positive effect of triptorelin on pain and bleeding are paralleled by the consistent suppression of circulating estradiol.

The present results, showing the beneficial effects of triptorelin on several symptoms, agree with the results of other recent studies (20, 21). Hot flushes and night sweats were the most common adverse events. However, these reactions were also quite common in the placebo group. These results are in accordance with data from a placebo-controlled study on leuprolide acetate (3). The rate of sleeping disorders was higher than generally reported for menopausal symptoms. However, results from a previous study with Decapeptyl Depot have indicated a high frequency of insomnia (20). Other symptoms associated with menopause, e.g., headache and arthralgia, did not occur more frequently during treatment with triptorelin than during placebo treatment. As in other studies (22, 23) the frequency of mood changes was moderately increased.

As 40 of the 48 patients who started therapy did not complete the 18 month-long study, the reasons for drop out are important. During treatment, the rate was the same. During follow-up, the drop-out rate was lower in the triptorelin group, in which negative reasons for drop out were less common than in the placebo group. Only 4 patients left the trial because of increased pain after triptorelin therapy compared to 16 patients after placebo.

Of the eight patients who dropped out because of pregnancy, five had received triptorelin. The number of drop outs during follow-up in this category of patients is high, above all because of the need for safe contraception or the desire to become pregnant, both reasons that could not be disregarded for ethical reasons. Thus, it is difficult to obtain a group of patients of sufficient size to study the recurrence pattern. In a French trial (20), only 7 patients out of 50 were lost to follow-up during the ensuing 6 to 12 months, so calculation of length of time to recurrence was easier. At least 11 patients in that study became pregnant, which is similar to the pregnancy rate in this trial, 21%.

In a placebo-controlled trial with leuprolide, patients with more advanced endometriosis participated (3). Forty-four percent of the patients had moderate or severe endometriosis compared with 8% in the present trial. This may explain why the drop-out rate in the placebo group was higher in the leuprolide trial. Although the two trials started with different populations, the follow-up results are similar in some ways. After leuprolide therapy, >30% of the patients had decreased dysmenorrhea and pelvic pain after 1 year of follow-up. In that trial, both groups of patients reported lower pain scores during and after treatment than before treatment. Adverse events were similar in the placebo and triptorelin groups.

A completely blinded study is not possible to perform in a study like the current one in which there are obvious different effects on menstrual bleeding patterns. However, the difference was not as obvious as could be expected, as some patients in the control group had bleeding disturbances during the study period and some who were receiving active treatment had bleeding, at least initially, so it was not obviously apparent during the study period to which group patients belonged.

In summary, this placebo-controlled study has shown that triptorelin effectively reduces pain related to endometriosis. The active treatment reduced the RAFS score by 50%, while there was an increase of 17% in the patient group given placebo.

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