FERTILITY AND STERILITY®
VOL. 82, NO. 5, NOVEMBER 2004

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

Add-back therapy in the treatment of endometriosis-associated pain

Errico Zupi, M.D.,[a] *Daniela Marconi, M.D., Ph.D.,*[b] *Marco Sbracia, M.D.,*[c] *Fulvio Zullo, M.D.,*[d] *Bonaventura De Vivo, M.D.,*[a] *Caterina Exacustos, M.D., Ph.D.,*[a] *and Giuseppe Sorrenti, M.D.*[e]

"Tor Vergata" University; San Giuseppe Hospital; Center for Endocrinology and Reproductive Medicine; Policlinico "Tor Vergata" Hospital, Rome; and Magna Graecia University, Catanzaro, Italy

Objective: To determine the efficacy of GnRH analogue plus add-back therapy compared with GnRH analogue alone and estroprogestin in patients with relapse of endometriosis-associated pain.

Design: Randomized, controlled study.

Setting: University hospital.

Patient(s): One hundred thirty-three women with relapse of endometriosis-related pain after previous endometriosis surgery.

Intervention(s): Forty-six women were treated with GnRH analogue plus add-back therapy, 44 women were given GnRH analogue alone, and 43 women received estroprogestin, for 12 months.

Main Outcome Measure(s): Pain evaluation by a visual analogue scale, quality of life in treated patients according to the SF-36 questionnaire, and occurrence of adverse effects, including bone mass density loss, at pretreatment, after 6 months of treatment, at the end of treatment (12 months), and 6 months after discontinuation of treatment.

Result(s): Patients treated either with GnRH analogue alone or GnRH analogue plus add-back therapy showed a higher reduction of pelvic pain, dysmenorrhea, and dyspareunia than patients treated with oral contraceptive, whereas patients treated with add-back therapy showed a better quality of life, as assessed with the SF-36 questionnaire, and adverse effects rate than the other two groups.

Conclusion(s): Add-back therapy allows the treatment of women with relapse of endometriosis-associated pain for a longer period, with reduced bone mineral density loss, good control of pain symptoms, and better patient quality of life compared with GnRH analogue alone or oral contraceptive. (Fertil Steril® 2004;82: 1303–8. ©2004 by American Society for Reproductive Medicine.)

Key Words: Endometriosis-related pain, medical treatment, GnRH analogue, add-back therapy, estroprogestin

Received November 21, 2003; revised and accepted March 15, 2004.

Reprint requests: Marco Sbracia, M.D., Center for Endocrinology and Reproductive Medicine, Via Carlo Porta 10, Rome 00153, Italy (FAX: 39-06-5880096; E-mail: marcandrea@hotmail.com).

[a] Department of Obstetrics and Gynecology, "Tor Vergata" University.

[b] San Giuseppe Hospital.

[c] Center for Endocrinology and Reproductive Medicine.

[d] Magna Graecia University.

[e] Policlinico "Tor Vergata" Hospital.

0015-0282/04/$30.00
doi:10.1016/j.fertnstert.2004.03.062

Endometriosis is a common gynecologic disease, affecting 5%–10% of reproductive-aged women in the general population (1). It is associated with pelvic pain, infertility, abnormal uterine bleeding, dysmenorrhea, and backache (2–4). The more severe forms of the disease are characterized by more intense symptomatology. After surgery or medical treatment, endometriosis recurs frequently in relation to disease severity in stages I and II (37%), and in stages III and IV it reaches a recurrence rate as great as 70% (5–8).

Low levels of estrogen are associated with regression of endometriosis lesions: hypoestrogenism might be obtained with a GnRH analogue (GnRH-a) with suppression of gonadotropin secretion by desensitization of the GnRH receptor in the hypophysis. Gonadotropin-releasing hormone analogues are widely used in the treatment of endometriosis symptoms because of their effectiveness in improving endometriosis-related symptoms. Treatment with these substances is generally limited to 6 months, owing to concern about the undesired effects of prolonged hypoestrogenism, such as osteoporosis (9). Supplementing GnRH-a treatment with estrogen and progestogen, or "add-back" therapy, has been suggested to overcome osteoporosis and climacteric symptoms associated with hypoestrogenism (10).

Several articles have been published reporting the results of various trials comparing treat-

ment with GnRH-a alone with GnRH-a plus add-back therapy (11–16), and though it is generally accepted that with 1 year of GnRH-a treatment add-back therapy is needed, there is no overall consensus among specialists as to the optimal add-back therapy (17). Furthermore, in a recent review of the literature (18), it was reported that GnRH-a therapy is as effective as the other treatments in pain control, and in another report it was shown that after a long follow-up there was no difference in bone loss between women treated with add-back therapy and those treated without (19).

To assess whether GnRH-a plus add-back therapy allows longer treatment, namely 12 months, and is associated with better pain control and quality of life than GnRH-a alone or oral contraceptive, we conducted a controlled study on women presenting with pain recurrence after surgery for endometriosis.

MATERIALS AND METHODS

The study was conducted at "Tor Vergata" University of Rome and approved by that institution's ethics committee and institutional review board. All patients referred to the Department of Obstetrics and Gynecology with recurrence of symptoms for endometriosis after previous surgery were invited to participate in the study. Patients eligible for study inclusion were women aged 20–43 years, with regular menstrual cycles, a history of symptomatic severe endometriosis diagnosed surgically according to the revised American Society for Reproductive Medicine classification (20), and recurrence of the disease with pelvic pain, dysmenorrhea, and dyspareunia. The study was conducted according to CONSORT statement guidelines. Of 211 patients assessed for eligibility during the study period, 150 who met the eligibility criteria agreed to participate. The patients were randomized by means of a computer-generated randomization number sequence. The number of 50 patients for each group was chosen to detect a difference between any two treatment regimens of 1.5, assuming a standard deviation of 0.5 for pelvic pain, dysmenorrhea, and dyspareunia (primary outcomes), with a power of 0.8 for $P<.05$. At the moment of randomization, four women included in group A, six women included in group B, and seven women included in group C refused the group to which they were allocated. From March 1, 2000 to February 28, 2003, 133 patients gave their written consent to the trial and were randomly allocated by means of a computer-generated randomization number sequence to three treatment groups: GnRH-a plus add-back therapy (group A), GnRH-a alone (group B), and estroprogestin alone (group C). Patients in group A (n = 46) received leuprolide acetate (Enantone Depot 11.25 mg; Takeda, Rome, Italy) every 3 months for 12 months plus transdermal E_2 (25 μg Esclima; Takeda) and daily oral norethindrone (5 mg Primolut-Nor; Schering, Berlin, Germany). Patients in group B (n = 44) received leuprolide acetate (Enantone Depot 11.25 mg; Takeda) every 3 months for 12 months. Patients in group C (n = 43) received oral ethinyl E_2 (30 μg) plus gestodene daily (0.75 mg Ginoden; Schering) for 12 consecutive months.

A complete medical, gynecologic, and drug history was taken. All patients underwent a clinical examination with ectocervical and endocervical smears, a pelvic and vaginal ultrasound scan, a diagnostic hysteroscopy with endometrial sampling, and a complete blood chemistry evaluation.

Quality-of-life and health-related satisfaction were assessed with the Medical Outcomes Survey Short Form 36 (SF-36), which is the most widely used generic instrument to evaluate health-related quality of life (21–25). It consists of eight domains (physical function, physical role function, emotional role function, social function, general health, mental health, vitality, and pain). The domain scores are rated so that higher values indicate better health (range, 0–100). The data were reported as mean ± standard deviation.

The degree of pain was measured according to a visual analog scale (VAS) for pelvic pain, dysmenorrhea, and dyspareunia. The VAS was administered to the patients by a nurse who was blind to the study before treatment, after 6 and 12 months of therapy, and 6 months after discontinuation of treatment.

Bone mineral density (BMD) of the lumbar spine (L1–L4) was measured by dual x-ray absorptiometry at prestudy, after 6 and 12 months of treatment, and 6 months after therapy discontinuation. All measurements were performed with the same machine (Hologic Quantitative Digital; Hologic MDM, Waltham, MA) according to standardized procedures. Results were expressed as grams per square centimeter.

The follow-up visits were at 6 months of treatment, after 12 months of treatment, and 6 months after discontinuation of therapy. The patients completed the SF-36 on quality-of-life issues, administered by a nurse blinded to the assigned treatment, before treatment, after 1 year of treatment, and at the follow-up 6 months after discontinuation of treatment.

Statistical analysis was performed with a commercial software program (SPSS for Windows; SPSS, Chicago, IL). For continuous variables, statistical significance was assessed with two-tailed Student's *t*-test for unpaired data in cases of normally distributed values, Mann-Whitney *U* test and Wilcoxon rank test in cases of non-normally distributed values, and one-way repeated-measures analysis of variance (ANOVA) or Friedman repeated-measures ANOVA of ranks. Pairwise post-hoc multiple comparisons were calculated with the Bonferroni correction for multiple comparisons or the Student-Newman-Keuls method. The χ^2 test and Fisher exact test were used when appropriate for discontinuous variables. $P<.05$ was defined as statistically significant.

TABLE 1

Demographic data, by group, of study patients and effects of treatments on pelvic pain, dysmenorrhea, and dyspareunia.

	Add-back (n = 46)	GnRH (n = 44)	Estroprogestin (n = 43)	*P*
Age (y)	35.8 ± 5.1	35.1 ± 4.8	36.1 ± 5.3	NS
Body mass index	26.9 ± 3.2	25.8 ± 3.3	26.4 ± 2.9	NS
Time free from disease (mo)	7.1 ± 3.1	6.2 ± 2.8	7.3 ± 2.7	NS
Stage of endometriosis, n (%)				
Stage III	26 (56.5)	25 (56.8)	22 (55.1)	NS
Stage IV	20 (43.5)	19 (43.2)	21 (44.9)	NS
Pelvic pain				
Pretreatment	6.9 ± 1.4	6.7 ± 1.2	6.3 ± 1.6	NS
After 6 mo	1.5 ± 0.4	1.3 ± 0.5	1.9 ± 0.8	.05
After 12 mo	0.3 ± 0.1	0.2 ± 0.1	0.8 ± 0.5	.01
6-mo follow-up	3.7 ± 2.7	3.2 ± 2.6	5.9 ± 2.5	.01
Dysmenorrhea				
Pretreatment	5.8 ± 1.6	6.1 ± 1.4	6.0 ± 1.8	NS
After 6 mo	0.0 ± 0.0	0.0 ± 0.0	1.9 ± 1.1	.01
After 12 mo	0.0 ± 0.0	0.0 ± 0.0	0.9 ± 0.5	.01
6-mo follow-up	3.1 ± 1.0	3.4 ± 1.2	4.9 ± 2.0	.01
Dyspareunia				
Pretreatment	5.8 ± 1.6	5.9 ± 1.5	5.6 ± 1.2	NS
After 6 mo	2.4 ± 1.6	2.6 ± 1.3	2.7 ± 1.5	NS
After 12 mo	1.2 ± 0.6	1.4 ± 0.5	1.3 ± 0.6	NS
6-mo follow-up	2.7 ± 1.5[a]	2.2 ± 1.1	3.9 ± 1.4[a]	.01[a]

Data are presented as mean ± SD, unless otherwise noted. Pelvic pain, dysmenorrhea and dyspareunia values are expressed in VAS units.
[a]Add-back versus estroprogestin.

Zupi. Add-back therapy for endometriosis. Fertil Steril 2004.

RESULTS

The three groups of patients were similar with respect to their demographic and clinical characteristics. There were no significant differences among the groups with regard to age, body mass index (BMI), stage of endometriosis, or period free from disease after surgery and before recurrence (Table 1).

No differences in baseline levels for pelvic pain were found among the groups. The GnRH-a plus add-back and GnRH-a alone groups had less pelvic pain than the oral contraceptive group at 6 and 12 months of treatment and 6 months after discontinuation of treatment ($P<.05$, $P<.01$, and $P<.01$, respectively). Data are shown in Table 1.

No differences in baseline levels for dysmenorrhea were found among the groups. The GnRH-a plus add-back and GnRH-a alone groups had less dysmenorrhea than the oral contraceptive group at 6 and 12 months of treatment, but also 6 months after discontinuation of treatment ($P<.01$ for all groups). Data are shown in Table 1.

For dyspareunia, no differences in baseline levels or at 6 and 12 months of treatment were found among the groups. The GnRH-a plus add-back and GnRH-a-alone groups had less dyspareunia than the oral contraceptive group 6 months after discontinuation of treatment ($P<.01$). Data are shown in Table 1.

Both GnRH-a-treated groups lost significant bone mineral density at 12 months of therapy and at 6 months' follow-up with respect to the baseline values and also with respect to the corresponding values observed in the oral contraceptive–treated patients ($P<.01$ and $P<.05$, respectively). However, the bone loss experienced by the women receiving add-back therapy was less than that experienced with GnRH-a alone ($P<.05$), and after 6 months' follow-up there was no difference in bone mineral density between the add-back therapy group and the oral contraceptive group. This was not the case, however, with the GnRH-a alone group, whose bone mineral density remained statistically significantly lower than that of the oral contraceptive group, both at the end of 12 months of therapy and after 6 months' follow-up ($P<.05$ and $P<.03$, respectively). The analysis of other adverse effects of treatment showed that the GnRH-a-alone group was affected by a higher rate of hot flashes ($P<.01$) and emotional change ($P<.05$) than the other two treatment groups, especially the add-back therapy group, which showed a rate of side effects similar to the oral contraceptive group. All data are reported in Table 2.

Table 3 reports the data regarding patient satisfaction with the treatment, evaluated with the SF-36. Patients treated with GnRH-a plus add-back therapy indicated a better quality of life than did the women of the other two groups, especially for pain control, vitality, general health, and physical func-

TABLE 2

Adverse events during treatment in patients treated with three different therapies.

	Add-back (n = 46)	GnRH (n = 44)	Estroprogestin (n = 43)
Bone mineral density, pretreatment (g/cm^2)	1.040 ± 0.111	1.050 ± 0.120	1.035 ± 0.112
Bone mineral density after 6 mo (g/cm^2)	1.010 ± 0.110	1.005 ± 0.112	1.040 ± 0.125
Bone mineral density after 12 mo (g/cm^2)	0.995 ± 0.102[a]	0.981 ± 0.099[b]	1.035 ± 0.121[c]
Bone mineral density after 6 mo follow-up (g/cm^2)	1.010 ± 0.091[d]	0.995 ± 0.110[e]	1.052 ± 0.132[f]
Hot flashes	26.1 (12)[g]	77.3 (34)	0.0 (0)[h]
Emotional changes	10.8 (5)	36.4 (16)[i]	6.9 (3)
Abnormal uterine bleeding	6.5 (3)	2.3 (1)	16.2 (7)
Other	4.3 (2)	9.1 (4)	11.6 (5)

Data are presented as mean ± SD.

[a] $P<.05$ vs. baseline.

[b] $P<.01$ vs. baseline.

[c] $P<.05$ vs. GnRH analogue alone after 12 months.

[d] $P<.03$ vs. baseline.

[e] $P<.03$ vs. baseline.

[f] $P<.03$ vs. baseline.

[g] $P<.01$ vs. GnRH analogue alone.

[h] $P<.01$ vs. GnRH analogue alone.

[i] $P<.05$ vs. add-back and estroprogestin.

Zupi. Add-back therapy for endometriosis. Fertil Steril 2004.

tion. The GnRH-a-alone group showed good satisfaction regarding only pain control, as did the GnRH-a plus add-back therapy group, but the values for general health, vitality, and physical function were similar to those of the oral contraceptive group.

DISCUSSION

The rationale for "add-back" therapy was proposed by Barbieri (26), who suggested the existence of an "estrogen threshold," below which estrogen is not able to stimulate endometriosis lesions and instead prevents hypoestrogenic side effects. Even though this threshold has not been defined in terms of E_2 levels, it has been reported that E_2 levels >40 pg/mL exacerbated the pain in patients treated with GnRH-a (6). Furthermore, another report showed that transdermal E_2 at a 25-μg dose plus medroxyprogesterone acetate as add-back therapy effectively suppressed hypoestrogenism side effects without the loss of anti-endometriosis effects (27). It

TABLE 3

Differences in the patients quality of life, as assessed by SF-36, before and after treatment.

	GnRH plus add-back (n = 46)			GnRH alone (n = 44)			Estroprogestin (n = 43)		
	Pre (A)	Post (B)	At 6 mo (C)	Pre (D)	Post (E)	At 6 mo (F)	Pre (G)	Post (H)	At 6 mo (I)
General health[a]	47.9 ± 12.7	59.6 ± 13.7	54.1 ± 12.1	49.4 ± 14.2	54.9 ± 12.7	51.6 ± 13.7	48.1 ± 12.1	51.2 ± 14.2	51.3 ± 13.0
Physical function[b]	52.6 ± 14.4	66.4 ± 15.1	60.8 ± 10.9	51.6 ± 13.2	57.6 ± 14	55.4 ± 15.1	52.8 ± 10.9	55.6 ± 13.2	54.2 ± 14.8
Role (physical)	58.3 ± 13.0	57.3 ± 14.8	56.3 ± 13.8	59.2 ± 15.4	60.1 ± 13.9	55.2 ± 13.4	57.1 ± 13.9	58.8 ± 12.0	54.2 ± 14.4
Role (emotional)	60.8 ± 12.0	60.0 ± 14.4	62.2 ± 14.4	60.5 ± 11.9	62.3 ± 15.2	60.8 ± 11.9	60.1 ± 15.2	58.1 ± 12.3	60.5 ± 14.8
Mental health	58.1 ± 12.3	60.5 ± 14.8	59.2 ± 14.4	59.8 ± 12.9	60.2 ± 13.6	59.7 ± 12.9	60.2 ± 13.6	59.4 ± 11.0	59.3 ± 12.2
Social function	56.4 ± 11.0	58.3 ± 12.7	60.2 ± 12.4	55.6 ± 9.7	54.5 ± 11.5	53.6 ± 9.7	58.5 ± 11.5	56.7 ± 11.0	57.0 ± 12.8
Vitality[c]	52.7 ± 11.0	68.0 ± 12.8	64.2 ± 14.4	53.4 ± 10.3	57.8 ± 11.3	56.3 ± 10.3	52.3 ± 11.3	56.1 ± 19.2	55.6 ± 17.0
Pain[d]	47.1 ± 19.2	63.6 ± 17.0	57.2 ± 11.4	46.4 ± 18.5	62.1 ± 14.0	58.4 ± 18.1	50.1 ± 14.0	58.3 ± 14.2	50.4 ± 18.5

Note: Pre = before treatment; Post = after treatment; At 6 mo = 6-mo follow-up.

[a] A vs. B, $P<.001$; A vs. C, $P<.02$.

[b] A vs. B, $P<.001$; A vs. C, $P<.01$; C vs. I, $P<.05$.

[c] A vs. B, $P<.05$; C vs. F, $P<.05$; C vs. I, $P<.05$.

[d] A vs. B, $P<.0001$; A vs. C, $P<.001$; D vs. E, $P<.0001$; D vs. F, $P<.01$; C vs. I, $P<.05$; F vs. I, $P<.05$.

Zupi. Add-back therapy for endometriosis. Fertil Steril 2004.

has also been showed that 5 mg daily of norethindrone plus 0.625 mg of equine conjugated estrogens as add-back therapy allowed good control of both the disease and hypoestrogenic side effects, without any important metabolic changes (28). On the basis of this evidence, we chose add-back therapy with transdermal estradiol 25 μg plus 5 mg of norethindrone daily to be administered for 12 months plus GnRH-a.

Our data, comparing three different treatments in patients with relapse of endometriosis-associated pain, suggested that GnRH-a treatment, alone or with add-back therapy, is more effective than oral contraceptive to induce a substantial remission of pain-associated symptoms, in addition to being better accepted by the patients, as shown by SF-36 data. Treatment with a GnRH-a considerably reduced the pain experienced by the patients for as long as 6 months after therapy had been discontinued. These data showed that GnRH-a is more effective in treating endometriosis recurrence, and it also should be considered as the treatment of choice for patients receiving more than 6 months of therapy, given its ability to abolish the pain. The side effects due to the long period of hypoestrogenism seem to be partially attenuated by the add-back therapy. Similarly to what has been reported from several studies (10–18), we observed that even though patients treated with GnRH-a plus add-back therapy showed a statistically significant BMD loss with respect to baseline levels, the loss was significantly less than that observed in women treated with GnRH-a alone for the same period of therapy. Furthermore, 6 months after treatment discontinuation, we observed higher levels of BMD in patients treated with add-back therapy than in women treated with GnRH-a alone, though both groups showed BMD levels that were still lower than baseline values. It is possible that a higher dose of E_2 might further prevent bone loss, but in our clinical experience, with 50 μg of transdermal E_2 patients often experience exacerbation of pain. However, it has been reported that even 6 years after discontinuation of GnRH-a treatment, BMD levels still remain lower than baseline values, independently of hormone replacement therapy treatment (19).

Moreover, the analysis of the data of the adverse effects in the patients treated with GnRH-a plus add-back therapy showed a lower incidence of hot flashes and mood change than in the group treated with GnRH-a alone. All these data showed that add-back therapy leads to better patient quality of life in cases of long-term therapy (1 year) with GnRH-a and also compared with oral contraceptive–treated women. When combined with add-back treatment, GnRH-a seems to be at least as effective as GnRH-a alone and significantly better than oral contraceptive to obtain remission of endometriosis-associated pain, whether pelvic pain, dysmenorrhea, or dyspareunia, in women with relapse of these symptoms after surgery. Furthermore, the lower rate of adverse effects found in women so treated suggests that this therapy should be considered the first-choice treatment in these patients, especially when long-term therapy is requested. Our study was focused on patient quality of life during treatment with these three different therapies; patient well-being was assessed with the SF-36, a questionnaire used worldwide in the routine assessment of patient satisfaction and their quality of life during treatments (21–25).

The data so obtained showed that GnRH-a plus add-back therapy was the most acceptable treatment, not only in terms of pain control, similar to GnRH-a alone, but also in terms of general health perception, vitality, and physical function. Estrogen administration in the patients with add-back therapy probably allows better quality of life. Estrogens in low doses significantly improved the perception of well-being and health, whereas GnRH-a alone, with complete suppression of estrogen activity, did not produce as high a perception of well-being. The same can be said for oral contraceptive alone, because its lesser degree of pain control did not give patients a substantial feeling of improvement in their general health, health function, and vitality. This is, to the best of our knowledge, the first study evaluating patient quality of life and self-perception of health during treatment.

From these observations, we conclude that add-back therapy allows the treatment of women with relapse of endometriosis associated-pain for a long period more safely, with limited BMD loss, good control of pain symptoms, and better quality of life compared with the other two treatments.

References

1. Wheeler J. Epidemiology of endometriosis-associated infertility. Reprod Med 1989;34:41–6.
2. Strathy JH, Molgaard CA, Coulam CB, Melton LJ 3rd. Endometriosis and infertility: a laparoscopic study of endometriosis among fertile and infertile women. Fertil Steril 1982;38:667–72.
3. Konnichs PR, Meuleman C, Demeyere S, Lesaffre E, Cornillie FJ. Suggestive evidence that pelvic endometriosis is a progressive disease, whereas deeply infiltrating endometriosis is associated with pelvic pain. Fertil Steril 1991;55:759–65.
4. Olive DL, Pritts EA. Treatment of endometriosis. N Engl J Med 2001;345:266–75.
5. Waller KG, Shaw RW. Gonadotrophin-releasing hormone analogues for the treatment of endometriosis: long-term follow-up. Fertil Steril 1993;59:511–5.
6. Hornstein MD, Yuzpe AA, Burry KA, Heinrichs LR, Buttram VL Jr, Orwoll ES. Prospective randomized double-blind trial of 3 versus 6 months of nafarelin therapy for endometriosis associated pelvic pain. Fertil Steril 1995;63:955–62.
7. Sutton CJ, Pooley AS, Ewen SP, Haines P. Follow-up report on a randomized controlled trial of laser laparoscopy in the treatment of pelvic pain associated with minimal to moderate endometriosis. Fertil Steril 1997;68:1070–4.
8. Winkel CA. Evaluation and management of women with endometriosis. Obstet Gynecol 2003;102:397–408.
9. American College of Obstetricians and Gynecologists. Clinical management guidelines for obstetrician-gynecologists. Medical management of endometriosis. ACOG Practice Bulletin number 11. Washington, DC: American College of Obstetricians and Gynecologists, 1999.
10. Surrey ES, Judd HL. Reduction of vasomotor symptoms and bone mineral density loss with combined norethindrone and long-acting gonadotropin-releasing hormone agonist therapy of symptomatic endometriosis: a prospective randomized trial. J Clin Endocrinol Metab 1992;72:558–63.
11. Friedman AJ, Hornstein MD. Gonadotropin-releasing hormone agonist plus estrogen-progestin "add-back" therapy for endometriosis-related pelvic pain. Fertil Steril 1993;60:236–41.
12. Kiilholma P, Tuimala R, Kivinen S, Korhonen M, Hagman E. Comparison of the gonadotropin-releasing hormone agonist goserelin acetate alone versus goserelin combined with estrogen-progestogen add-back therapy in the treatment of endometriosis. Fertil Steril 1995;64:903–8.

13. Surrey ES, Voigt B, Fournet N, Judd HL. Prolonged gonadotropin-releasing hormone agonist treatment of symptomatic endometriosis: the role of cyclic sodium etidronate and low-dose norethindrone "add-back" therapy. Fertil Steril 1995;63:747–55.
14. Lindsay PC, Shaw RW, Bennink HJ, Kicovic P. The effect of add-back treatment with tibolone (Livial) on patients treated with the gonadotropin-releasing hormone agonist triptorelin (Decapeptyl). Fertil Steril 1996;65:342–8.
15. Moghissi KS, Schlaff WD, Olive DL, Skinner MA, Yin H. Goserelin acetate (Zoladex) with or without hormone replacement therapy for the treatment of endometriosis. Fertil Steril 1998;69:1056–62.
16. Franke HR, van de Weijer PH, Pennings TM, van der Mooren MJ. Gonadotropin-releasing hormone agonist plus "add-back" hormone replacement therapy for treatment of endometriosis: a prospective, randomized, placebo-controlled, double-blind trial. Fertil Steril 2000;74:534–9.
17. Surrey ES. Add-back therapy and gonadotrophin-releasing hormone agonists in the treatment of patients with endometriosis: can a consensus be reached? A Back Consensus Working Group. Fertil Steril 1999;71:420–4.
18. Prentice A, Deary AJ, Goldbeck-Wood S, Farquhar C, Smith SK. Gonadotrophin-releasing hormone analogues for pain associated with endometriosis. Chochrane Database Syst Rev 2000;(2):CD000346.
19. Pierce JS, Gazvani R, Farquharson RG. Long-term use of gonadotrophin-releasing hormone analogs and hormone replacement therapy in the management of endometriosis: a randomized trial with a 6-year follow-up. Fertil Steril 2000;74:964–8.
20. American Society for Reproductive Medicine. Revised American Society for Reproductive Medicine classification of endometriosis: 1996. Fertil Steril 1997;67:817–21.
21. Ware JE, Sherbourne CD. The MOS 36-Item Short Form Health Survey (SF-36), I: conceptual framework and item selection. Med Care 1992;30:473–83.
22. Aaronson NK, Acquadro C, Alonso J, Apolone G, Bucquet D, Bullinger M. International quality of life assessment (IQOLA) project. Qual Life Res 1992;1:349–51.
23. McHorney CA, Ware JE, Raczek AE. The MOS 36-Item Short Form Health Survey (SF-36), II: psychometric and clinical tests of validity in measuring physical and mental health constructs. Med Care 1993;31:247–63.
24. Jenkinson C, Coulter A, Wright L. Short Form 36 (SF36) health survey questionnaire: normative data for adults of working age. BMJ 1993;306:1437–40.
25. Apolone G, Mosconi P. The Italian SF-36 Health Survey: translation, validation and norming. J Clin Epidemiol 1998;51:1025–36.
26. Barbieri RL. Hormone treatment of endometriosis: the estrogen threshold hypothesis. Am J Obstet Gynecol 1992;166;740–5.
27. Howell R, Edmonds D, Dowsett M, Crook D, Lees B, Stevenson J. Gonadotropin-releasing hormone analogue (goserelin) plus hormone replacement therapy for the treatment of endometriosis: a randomized clinical trial. Fertil Steril 1995;64:474–81.
28. Honstein MD, Surrey ES, Weisberg GW, Casino LA. Leuprolide acetate depot and hormonal add-back in endometriosis: a 12 months study. Obstet Gynecol 1998;91:16–24.