

The following abstracts, from medical journals containing literature on endometriosis and chronic pelvic pain, were selected for their relevance to this Special Report supplement.

GnRH Agonist as Empiric Treatment of Pelvic Pain

Chronic pelvic pain is a common and confounding complaint for which many clinicians quickly proceed to diagnostic laparoscopy. A more conservative approach is the use of gonadotropin-releasing hormone agonist (GnRH agonist) as presumptive treatment when malignancy has been ruled out and endometriosis is suspected. A 2- or 3-month trial is recommended, followed by completion of the full 6-month course if empiric therapy provides relief, or by laparoscopy if it does not. Advantages of empiric therapy include lower cost, the preference of most patients for medical therapy over surgery for chronic, non-life-threatening conditions, and outcomes that are comparable to or better than those for surgery. A trial of empiric therapy with a GnRH agonist provides patients with maximum benefit at minimal risk for a reasonable cost. This approach is appropriate when endometriosis is the suspected cause of chronic pelvic pain.

Lindheim, Steven R. Using Gn-RH-a to treat pelvic pain empirically. *OBG Management* November 1996:25-36.

Study Results of Depot Leuprolide Treatment of Chronic Pelvic Pain and Endometriosis

The investigators for this 12-site US study compared the gonadotropin-releasing hormone agonist (GnRH agonist), depot leuprolide, with placebo in managing chronic pelvic pain in women with clinically suspected endometriosis. A diagnostic algorithm comprised of extensive, noninvasive diagnostic testing and laboratory evaluation was used to identify subjects. One hundred women between the ages of 18 and 45 with clinically suspected endometriosis were randomized into the double-blind trial, with 49 in the depot leuprolide group (3.75 mg/mo) and 46 in the placebo group completing the study. Treatment for both groups involved intramuscular administration 3 times at 4-week intervals. At week 12, women in the depot leuprolide group had statistically and clinically significant mean improvements in pain from baseline compared with those of women in the placebo group. Posttreatment laparoscopies confirmed endometriosis in 78% of the depot leuprolide subjects and 87% of the placebo subjects. The investigators concluded that a GnRH agonist can be used safely and effectively after an extensive pretreatment diagnostic work-up to clinically diagnose endometriosis and provide pain relief to patients. They noted that research on the empiric use of depot leuprolide should continue.

Ling FW, for the pelvic pain study group. Randomized controlled trial of depot leuprolide in patients with chronic pelvic pain and clinically suspected endometriosis. *Obstet Gynecol* 1999;93(1):51-58

Benefits of GnRH-a After Negative Laparoscopy

Endometriosis, the most common cause of chronic pelvic pain, is difficult to diagnose. Although many gynecologists consider laparoscopy to be the diagnostic gold standard for endometriosis, many factors affect its accuracy: the surgeon's skill and experience, the thoroughness of the examination, and the appearance of the endometriotic implants, which vary markedly in appearance and location. Deep, subtle, and microscopic lesions are particularly difficult to detect laparoscopically. Thus, even after a negative laparoscopy, endometriosis remains the most likely diagnosis. Gonadotropin-releasing hormone agonists (GnRH agonists) have been well documented to relieve the signs and symptoms of endometriosis. Relief of pain after 2 or 3 months of treatment with a GnRH agonist has been used in presumptive diagnosis of endometriosis instead of laparoscopy. When history, physical examination, laboratory and imaging studies, and laparoscopy have eliminated other causes of chronic pelvic pain, short-term empiric therapy with a GnRH agonist provides an effective option for physicians and patients who would otherwise have few alternatives.

Scialli AR. Using GnRH-a following a negative laparoscopy. *OBG Management* December 1998:41-49

Quality-of-Life and Economic Benefits of GnRH-a

In this review of multicenter, placebo-controlled, clinical trials of gonadotropin-releasing hormone agonist (GnRH-a), the researchers investigated the effects on signs and symptoms of 3 versus 6 months of therapy; 3 months of retreatment; and 3 months of postoperative treatment. Early clinical trials of GnRH-a lasted 6 months and demonstrated prompt symptom relief, often within 4 to 8 weeks of starting therapy. This led to 3-month trials that demonstrated levels of pain relief and reduction in clinical signs similar to those in the 6-month trials. Trials of retreatment for recurrent symptoms demonstrated the same reduction in symptoms as the initial therapy. Other trials demonstrated that combining laparoscopy with postoperative GnRH-a produced longer symptom relief than surgery alone. Side effects are significantly less frequent after 3 months of GnRH-a than after 6 months. The medical approach is considerably less expensive than surgery. The researchers concluded that a 3-month course of GnRH-a could be cost effective in the presumptive diagnosis and treatment of endometriosis.

Heinrichs WLR, Henzl MR. Human issues and medical economics of endometriosis. *J Reprod Med* 1998;43(suppl 3):299-308.

Quality-of-Life Questionnaire for Patients With Endometriosis

Few studies have been conducted to assess the functioning and well-being of women with endometriosis. This study evaluated a new health-related quality-of-life (HRQOL) instrument with 95 generic and endometriosis-targeted scales and items. One hundred and thirty-seven women with endometriosis participated: 122 were enrolled in a multicenter, open-label, randomized, parallel-design, Phase III clinical trial of leuprolide acetate therapy and 15 were from a private gynecologic practice. The women in the Phase III trial completed the self-administered questionnaire 4 times (at screening, baseline, and weeks 12 and 24); those in private practice completed it twice (approximately 1 week apart). The results indicated that reproducibility and reliability were acceptable, construct validity was demonstrated, HRQOL varied in a manner consistent with clinician-rated and patient-reported measures, and the questionnaire was responsive to change. The researchers concluded that this is the first reliable, valid, and responsive HRQOL study for endometriosis patients. A limitation of the study is that reproducibility was measured in private practice, and the results may not be generalizable because of the small and heterogeneous sample.

Colwell HH, Mathias SD, Pasta DJ, Henning MJ, Steege JF. A health-related quality-of-life instrument for symptomatic patients with endometriosis: A validation study. *Am J Obstet Gynecol* 1998;179(1):47-55.

Add-Back Therapy Following GnRH-a Treatment

The effects of hormone add-back therapy in endometriosis patients treated with gonadotropin-releasing hormone agonist (GnRH-a) were assessed in this prospective, double-blind, randomized, placebo-controlled study conducted at the University of Düsseldorf, Germany. Twenty-seven patients with endometriosis confirmed by laparoscopy were enrolled in the 6-month trial. All patients received a monthly intramuscular injection of 3.75-mg leuprolide acetate. Fourteen patients in the GnRH-a + add-back group also received 1 tablet daily of ethinyl estradiol 20 µg with desogestrel 0.15 mg, and 13 patients in the GnRH-a + placebo group received placebo daily. At baseline, bone mineral density (BMD), urine pyridinoline levels, and serum calcium levels were comparable between the groups. The results demonstrated significant improvements in endometriosis, dysmenorrhea, and pelvic pain in both groups, but these improvements were significantly better in the GnRH-a group. The placebo group had significantly greater loss of lumbar spine BMD and higher serum calcium levels and urinary pyridinium crosslinks. The add-back therapy protected women taking GnRH-a from severe BMD loss and accelerated bone collagen resorption, but it reduced the efficacy of the GnRH-a. The investigators concluded that additional prospective studies with new hormone add-back strategies or bone protection medication are needed.

Gnoth C, Gödtke K, Freundl G, Godehardt E, Kienle E. Effects of add-back therapy on bone mineral density and pyridinium crosslinks in patients with endometriosis treated with gonadotropin-releasing hormone agonists. *Gynecol Obstet Invest* 1999;47:37-41.

Benefits of Combined Treatment of Endometriosis

In addition to its use as primary therapy, gonadotropin-releasing hormone agonist (GnRH-a) therapy is now used as an adjuvant to laparoscopy. This article summarizes the literature on the use of GnRH-a in conjunction with laparoscopy and provides treatment recommendations. While the clinical impression is that preoperative GnRH-a facilitates surgery by decreasing the extent of endometriosis and the inflammatory reaction and blood supply to implants, thus decreasing operating time and blood loss, no objective data support this impression. For ovarian endometriomas, preoperative GnRH-a is associated with reductions in the size of endometriomas and the surrounding inflammatory reactions, which may facilitate surgery. Transvaginal ultrasound-directed drainage followed by 8 weeks of GnRH-a for very large endometriomas may allow surgeons to replace laparotomy with laparoscopy, but further studies are necessary. After laparoscopy, GnRH-a use prevents recurrence of pain and increases the delay before alternative treatments or repeat surgery. The author concluded that most patients would benefit from post-operative GnRH-a therapy.

Hemmings R. Combined treatment of endometriosis: GnRH agonists and laparoscopic surgery. *J Reprod Med* 1998;43(suppl 3):316-319

Study Results on Triptorelin Use in Endometriosis Treatment

Few studies on the effect of gonadotropin-releasing hormone agonists (GnRH-a) compared to placebo have been done. This study, conducted at 3 hospitals (2 university and 1 general) in Sweden, compared the effect of triptorelin to placebo in 49 women with endometriosis. The 18-month, prospective, randomized, double-blind study included 6 months of treatment and 12 months of follow-up. Twenty-four patients in the active control group received monthly injections of triptorelin depot; 25 received placebo. Treatment efficacy was evaluated by changes in symptoms, visible endometriosis extension, and frequency and amount of bleeding. Three patients (1 active control, 2 placebo) dropped out during the treatment period. After 2 months, pain symptoms were significantly lower in the triptorelin-treated patients than in the placebo-treated patients. Endometriotic lesions decreased by 50% in the triptorelin group and increased by 17% in the placebo group. The average area of endometriotic lesions decreased by 45% in the triptorelin group and remained the same for the placebo group. These results confirmed those of previous studies. During follow-up, most patients dropped out, with only 8 patients (5 triptorelin and 3 placebo) completing the 18-month trial. The researchers concluded that triptorelin reduces lesion size and pain levels significantly more than placebo does.

Bergqvist A, Bergh T, Hogström L, Mattsson S, Nordenskjöld F, Rasmussen C. Effects of triptorelin versus placebo on the symptoms of endometriosis. *Fertil Steril* 1998;69(4):702-707.

Diagnosing Cause of Chronic Pelvic Pain as Endometriosis

Determining when chronic pelvic pain is caused by endometriosis is difficult. This article outlines 3 criteria that should be met before attributing chronic pelvic pain to endometriosis: cyclic pelvic pain, a surgical diagnosis of endometriosis, and prolonged pain relief after medical or surgical treatment. These criteria are based on characteristics identified in clinical trials. Cyclic pelvic pain, dysmenorrhea with pelvic pain, and dyspareunia exacerbated before and during menses are common symptoms in endometriosis. Surgical diagnosis is necessary because medical therapy, such as GnRH-a, also relieves other types of pain and may result in overdiagnosis of endometriosis. Pain relief after medical or surgical treatment suggests that pain is caused by endometriosis. These evidence-based criteria can help physicians accurately identify women with symptomatic endometriosis, resulting in the development of more effective treatments. They serve to remind physicians that endometriosis can be asymptomatic and that pain has many other causes. These criteria can also help prevent delays in diagnosing and treating the real cause of pain, and help determine which women are more likely to experience pain relief with hysterectomy.

Hurd WW. Clinical commentary: Criteria that indicate endometriosis is the cause of chronic pelvic pain. *Obstet Gynecol* 1998;92(6):1029-1032.

Laparotomy Versus Laparoscopy

This study compared laparotomy to laparoscopy to determine which is better for treatment of recurrent endometriosis. Eighty-one women who underwent reoperation at the Universities of Milan and Verona in Italy, between 1986 and 1996, were enrolled. The groups were comparable at baseline for age, interval between the operations, disease stage at reoperation, chief complaint, infertility factors, and concomitant diseases. At the original surgery, 50 women underwent laparotomy and 31 laparoscopy; at the second surgery, 41 women underwent laparotomy and 40 laparoscopy. After the second operation, clinical and ultrasound examinations were performed at least annually to evaluate the recovery of fertility and the reappearance of endometriosis symptoms and signs; the laparotomy group was followed longer (54.1 ± 30.1 months) than the laparoscopy group (20.8 ± 10.2 months). Both the dyspareunia recurrence rate and the number of women requiring a third operation were higher in the laparotomy group. No significant difference was observed between the groups in pregnancy rates at 24 months. While researchers noted this was not a randomized study, and that the sample size was relatively small, they concluded that laparoscopy was as efficacious as laparotomy in treating recurrent endometriosis.

Busacca M, Fedele L, Bianchi S, et al Surgical treatment of recurrent endometriosis: Laparotomy versus laparoscopy. *Hum Reprod* 1998;13(8):2271-2274.

Leuprolide Acetate Depot Alone and in Combination With Add-Back Therapy

This multicenter, randomized, double-blind, 1-year clinical trial evaluated the efficacy and safety of gonadotropin-releasing hormone agonist (GnRH-a) therapy (leuprolide acetate depot) alone and with 3 separate add-back regimens. The study included 201 symptomatic endometriosis patients assigned to 4 treatment groups. All women received an intramuscular injection of leuprolide acetate depot 3.75 mg every 4 weeks. Group A also received placebo; Group B received norethindrone acetate 5 mg daily and placebo; and Groups C and D received norethindrone acetate 5 mg with conjugated equine estrogens (0.625 and 1.25 mg daily, respectively). The groups were similar in baseline characteristics, mean dysmenorrhea scores, nonmenstrual pelvic pain, and bone mineral density (BMD) of the lumbar spine. All groups showed significant relief of pelvic pain by week 8. Group D had the highest drop-out rate because of lack of improvement. Only patients in Group A experienced loss of BMD. One hundred twenty patients (60%) completed the trial. The researchers concluded that the use of leuprolide acetate depot combined with norethindrone acetate 5 mg alone or with conjugated equine estrogen 0.625 effectively suppresses pelvic pain while protecting against bone loss. These add-back therapies make prolonging GnRH-a therapy for up to 1 year safe and effective.

Hornstein MD, Surrey ES, Weisberg GW, Casino LA. Leuprolide acetate depot and hormonal add-back in endometriosis: A 12-month study. *Obstet Gynecol* 1998;91(1):16-24.