Medical Therapy of Endometriosis

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ABSTRACT

The medical treatment of endometriosis is a critical aspect of the therapeutic approach to this disease. Past methods have been based upon systemic hormonal alterations, resulting in suppression of this estrogen-responsive disorder. Treatments such as danazol, progestogens, oral contraceptives, GnRH-agonists, and gestrinone achieve their effects upon endometriosis via this method. However, with a growing understanding of the pathogenesis of this disease, more precise molecular targets for treatment have been identified. Thus, a series of newer agents are under development and hold the potential of greater efficacy and flexibility than traditional treatments. This review analyzes the available and experimental medical treatments of endometriosis, their utility in the treatment of pain and infertility, and their role in the future.

KEYWORDS: Endometriosis, medical therapy, infertility, pelvic pain, review

The development of medication to treat endometriosis was originally built upon several observations. First, endometriosis is encountered infrequently in the parous woman but much more often in the nulliparous female, suggesting a protective effect of the hormonal milieu of pregnancy. Second, endometrium is known to be estrogen dependent, with ectopic endometrium presumably behaving in much the same manner. Finally, endometriosis tends to occur nearly exclusively in menstruating, reproductive age women, again suggesting hormonal dependence. These findings suggested the potential benefits of hormonal therapy to alter the normal menstrual cyclicity of the reproductive years, the mainstay of medical treatment for endometriosis.

Recently, however, the approach has changed. We now have a much greater depth of understanding of the pathogenesis, growth, and maintenance of ectopic endometrium, particularly at the molecular level. This has provided drug developers with precise molecular targets for treatment of the disease. Currently under development, these newer agents hold the potential of greater efficacy and flexibility with fewer systemic effects.

ESTABLISHED MEDICAL TREATMENTS OF ENDOMETRIOSIS

Danazol

The first drug to be approved for the treatment of endometriosis in the United States was danazol, an isoxazol derivative of 17α-ethinyl testosterone. It was originally thought to produce a pseudomenopause, but subsequent studies have shown that the drug acts primarily by diminishing the midcycle luteinizing hormone (LH) surge,[1,2] creating a chronic anovulatory state. Additional actions include inhibition of multiple enzymes in the steroidogenic pathology[3] and an increase in free serum testosterone.[4] The recommended dosage of danazol for the treatment of endometriosis is 600 to 800 mg/day; however, these doses have substantial androgenic side effects such as increased hair growth, mood changes, adverse serum lipid profiles, deepening of the voice (possibly irreversible), and, rarely, liver damage (possibly irreversible and life-threatening) and arterial thrombosis.[5,6] Studies of lower doses as primary treatment for endometriosis-associated pain have been uncontrolled

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or contained small numbers of patients and thus are of limited value.[7]

Because of the many side effects of the drug, alternative routes of administration have been sought. Recently, the use of danazol vaginal suppositories[8] and a danazol-impregnated vaginal ring[9] has been described in small, uncontrolled trials. Preliminary results suggest that the side effects may be less severe with the transvaginal approach.

Progestogens

Progestogens are a class of compounds that produce progesterone-like effects upon endometrial tissue. A large number of progestogens exist, ranging from those chemically derived from progesterone (progestins) such as medroxyprogesterone acetate (MPA) to 19-nortestosterone derivatives such as norethindrone and norgestrel. The proposed mechanism of action of these compounds is initial decidualization of endometrial tissue followed by eventual atrophy. This is believed to be due to a direct suppressive effect of progestogens upon the estrogen receptors of the endometrium. There is evidence suggesting that another mechanism of action at the molecular level is the suppression of matrix metalloproteinases, enzymes important in the implantation and growth of ectopic endometrium.[10]

The most extensively studied progestational agent for the treatment of endometriosis is medroxyprogesterone. The drug was originally used orally for the treatment of endometriosis, with doses ranging from 20 to 100 mg daily; published randomized studies are limited to 100 mg daily. However, the depot formulation has also been used, in a dose of 150 mg every 3 months. Side effects of medroxyprogesterone are multiple and varied. A common side effect is transient breakthrough bleeding, which occurs in 38 to 47%. This is generally well tolerated and, when necessary, can be adequately treated with supplemental estrogen or an increase in the progestogen dose. Other side effects include nausea (0 to 80%), breast tenderness (5%), fluid retention (50%), and depression (6%).[11] In contradistinction to danazol, all of the adverse effects mentioned resolve upon discontinuation of the drugs.

Norethindrone acetate has also been utilized as a treatment for endometriosis. This 19-nortestosterone derivative has been analyzed only in a retrospective, uncontrolled trial of 52 women.[12] Each was treated initially with 5 mg daily, with increases of 2.5-mg increments up to a maximum dose of 20 mg daily until amenorrhea was achieved. Side effects were similar to those seen with medroxyprogesterone.

Other progestational agents have also been used in the occasional study, including lynestrenol, a gestagen used primarily in Europe. Levonorgestrel, the active ingredient of Norplant, has also been utilized recently via an intrauterine delivery system.[13] The drug has been shown to decrease effectively vascular endothelial growth factor (VEGF) and blood vessel proliferation, providing a rationale for its use in endometriosis.[14] It has been touted as a desirable treatment for rectovaginal endometriosis, although evidence thus far is uncontrolled and scant.[13]

Progestogens may adversely affect serum lipoprotein levels. The 19-nortestosterone derivatives significantly decrease high-density lipoprotein (HDL) cholesterol.[15] Data on MPA are less clear, with studies demonstrating either no effect[16] or a slight decrease.[17] It is likely that there is a decrement in HDL with all these agents, but the magnitude is related to the specific progestogen and the dose administered. Whether alterations in serum lipoprotein levels for 4 to 6 months have any clinical significance is unclear.

Oral Contraceptives (Combination Estrogen-Progestogen)

The combination of estrogen and progestogen for therapy of endometriosis, the so-called pseudopregnancy regimen, has been utilized for 40 years. As with progestational therapy alone, pseudopregnancy is believed to produce initial decidualization and growth of endometrial tissue, followed in several months by atrophy. This has been observed in women[18] but is in direct conflict with data from the rhesus monkey demonstrating larger implants with considerable local growth following such a therapeutic approach.[19]

Pseudopregnancy regimens have been administered both orally and parenterally. Combination oral contraceptive pills such as norethynodrel and mestranol, norethindrone acetate and ethinyl estradiol, lynestrenol and mestranol, and norgestrel plus ethinyl estradiol have all been tried. Parenteral combinations have included 17-hydroxyprogesterone or depot MPA paired with stilbestrol or conjugated estrogens.

Side effects of pseudopregnancy are often quite impressive and include those encountered with progestogens alone as well as estrogenic- and androgenic-related effects. Estrogens may cause nausea, hypertension, thrombophlebitis, and uterine enlargement. The 19-nortestosterone–derived progestogens may cause androgenic effects such as acne, alopecia, increased muscle mass, decreased breast size, and deepening of the voice. Noble and Letchworth,[20] in a comparative trial of norethynodrel and mestranol versus danazol, found that 41% of the pseudopregnancy group failed to complete their course of therapy because of side effects of the medication. However, dosages used in this study were quite high compared with those in modern contraceptive preparations. The oral contraceptives commonly prescribed today for combination therapy are most likely to produce a progestogen-dominant picture similar to that of progestogen alone.

Today, oral contraceptives are the most commonly prescribed treatment for endometriosis symptoms. Despite this, there are few data regarding mechanism of action. One investigation suggested that oral contraceptives suppress proliferation and enhance programmed cell death (apoptosis) in endometrial tissue, perhaps providing a mechanistic clue to the action of these drugs.[21]

GnRH Agonists

Gonadotropin-releasing hormone (GnRH) agonists are modified forms of GnRH that bind to the pituitary GnRH receptors and remain for a lengthy time. They are thus identified by the pituitary as rapidly pulsatile GnRH and, after initial stimulation of follicle-stimulating hormone and LH secretion, result in a down-regulation of pituitary gonadotropin secretion. The result is a lack of ovarian stimulation and a hypoestrogenic state similar to that of menopause, producing endometrial atrophy and amenorrhea. It is also possible that the drug affects ectopic endometrium via additional mechanisms; animal studies have suggested alterations in plasminogen activators and matrix metalloproteinases, factors important in endometriosis development.[22]

The agonist can be given intranasally, subcutaneously, or intramuscularly depending upon the specific product, with frequency of administration ranging from twice daily to every 3 months. The side effects are those of hypoestrogenism such as transient vaginal bleeding, hot flashes, vaginal dryness, decreased libido, breast tenderness, insomnia, depression, irritability and fatigue, headache, osteoporosis, and decreased skin elasticity; these are dose dependent.[23]

A modification of GnRH agonist treatment is to "add back" small amounts of steroid hormone in a manner similar to that used in the treatment of postmenopausal women. The theory is that the requirement for estrogen is greater for endometriosis than for the brain (to prevent hot flashes), the bone (to prevent osteoporosis), and other tissues deprived of this hormone.[24] Interestingly, this "threshold hypothesis" appears to be true, with estrogen-progestogen or progestogen only add-back therapy resulting in an equivalent rate of pain relief with far fewer side effects than GnRH agonist alone. Estrogen as a solitary add-back, however, is less effective and thus inadvisable.[25] Currently, only levonorgestrel add-back therapy has been approved by the Food and Drug Administration, although regimens of conjugated estrogens and medroxyprogesterone have also been demonstrated to be effective.

Gestrinone

Gestrinone (ethylnorgestrienone, R2323) is an antiprogestational steroid used extensively in Europe for the treatment of endometriosis but not currently available in the United States. Its effects include androgenic, antiprogestogenic, and antiestrogenic actions, although the latter are not mediated by estrogen receptor binding.

This steroid is believed to act by inducting a progesterone withdrawal effect at the endometrial cellular level, thus enhancing lysosomal degradation of the cellular structure. There is a rapid decrease in estrogen and progesterone receptors in normal endometrium following administration of gestrinone, as well as a sharp increase in 17β-hydroxysteroid dehydrogenase. Interestingly, these cellular effects did not occur in samples of endometriotic tissue.[26]

Gestrinone may also inhibit ovarian steroidogenesis. A 50% decrease in serum estradiol level is noted after administration, perhaps related to the associated significant decline in sex hormone–binding globulin concentration (an androgenic or antiprogestogenic effect).[27]

Gestrinone is administered orally in doses of 2.5 to 10 mg weekly, on a daily, twice-weekly, or three-times-weekly schedule. Side effects include androgenic and antiestrogenic sequelae. Although most side effects are mild and transient, several, such as voice changes, hirsutism, and clitoral hypertrophy, are potentially irreversible.

EXPERIMENTAL MEDICAL TREATMENTS OF ENDOMETRIOSIS

RU486 (Mifepristone) and Selective Progesterone Receptor Modulators

Apart from its controversial role in pregnancy termination, mifepristone (RU486) may well prove to be of value in a wide variety of gynecologic disorders, including endometriosis. The drug is an antiprogesterone and antiglucocorticoid that can inhibit ovulation and disrupt endometrial integrity. When used in the treatment of endometriosis doses of the medication range from 50 to 100 mg daily, with side effects ranging from hot flashes to fatigue, nausea, and transient liver transaminase changes. No effect upon lipid profiles or bone mineral density have been reported.

The ability of mifepristone to produce a regression of endometriotic lesions has been variable and apparently dependent upon duration of treatment. Trials of 2 months in the rodent model[28] and 3 months in the human[29] failed to produce regression of disease. However, 6 months of therapy resulted in less visible disease in women (L.M. Kettel, A.A. Murphy, A.J. Morales, et al, unpublished data).

Uncontrolled trials suggest possible efficacy for endometriosis-associated pain, although numbers are small.[29] No data have yet been collected regarding fertility enhancement.

Selective progesterone receptor modulators (SPRMs) are partial antagonists of progesterone that also behave like progesterone in some tissues. This mixed ago-

nist-antagonist effect may prove valuable if an SPRM can inhibit endometrial growth while not producing other systemic effects of progesterone, such as breast tenderness, depression, and fluid retention. The mesoprogestin J867 is currently in phase III clinical trials; early studies have suggested efficacy in pain relief with minimal side effects.

Selective Estrogen Receptor Modulators

Selective estrogen receptor modulators (SERMs) are molecules similar to estrogen that behave like an estrogen in some tissues but as an estrogen antagonist in other locations. Given the need for estrogen exposure to promote endometriosis growth and development, the development of an SERM that acts as an antagonist of estrogen at the endometrium but as an agonist elsewhere would be of therapeutic value. Raloxifene fits this profile to some extent: the molecule inhibits endometrial growth while promoting bone growth. However, the antagonistic action is not limited to endometrium, as vasomotor symptoms indicative of estrogen deficiency may also occur with this drug. Additional SERMs are currently under development in an attempt to find the "ideal" agonist-antagonist profile.

GnRH Antagonists

Like GnRH agonists, the class of drugs called GnRH antagonists are analogs of GnRH that cause a down-regulation of the pituitary gland, a reduction of gonadotropin secretion, and suppression of ovarian steroid production. Unlike GnRH agonists, however, these drugs do not cause an initial stimulation of gonadotropin and ovarian hormone release. Thus, they may have the advantage of working faster and more effectively, with better patient compliance because of earlier amelioration of symptoms. Studies in animal models of endometriosis have been quite promising,[30] and preliminary clinical trials suggest that the drug is safe and efficacious (P.M. Martha, M.E. Gray, M. Campion, et al, unpublished data). An investigation in women demonstrated that a GnRH antagonist improved the health-related quality of life in women with endometriosis.[31] Phase III clinical trials are ongoing to validate further the use of this medication for endometriosis, as questions regarding relative efficacy and rate of side effects compared with GnRH agonists must be answered.

Aromatase Inhibitors

Recent investigation has shown that endometriosis is capable of producing its own estrogen because of the presence of aromatase with the implant.[32] This enzyme, not found in normal endometrium, is stimulated by prostaglandin E_2 (PGE_2); the resulting estrogen production then stimulates PGE_2, further enhancing estrogen production. This cascade provides a potential therapeutic target for the treatment of endometriosis: inhibiting the aromatization process might result in endometriosis implants thriving less readily.

Aromatase inhibitors have now been tested in the rodent endometriosis model with good success.[33] In addition, a case report of the use of anastrazole in a postmenopausal woman with severe endometriosis suggests the potential value of this treatment in women.[32] However, substantial bone loss in this woman emphasizes the need for caution with this class of medications and reinforces the value of larger clinical trials to determine safety and efficacy.

TNF-α Inhibitors

Tumor necrosis factor (TNF)-α is a cytokine that appears to be overproduced in endometriosis patients and may well be at least partially responsible for the influx of peritoneal macrophages known to occur in women with this disease. One therapeutic approach that has been considered is blockade of this cytokine. This has been attempted in the baboon, where recombinant human TNF binding protein-1 (TBP-1) was mixed with menstrual endometrium prior to seeding the peritoneal cavity with the tissue.[34] In this experiment, endometriosis development was inhibited. In addition, baboons with endometriosis were treated with TBP-1, GnRH antagonist, or placebo; significantly less endometriosis was noted with TBP-1 and GnRH antagonist treatment. These studies suggest that TBP-1 is effective in treating the physical manifestations of endometriosis in the baboon and may be of value in the human. Clinical trials, however, have yet to be conducted.

Angiogenesis Inhibitors

Several angiogenic factors have been found to be present in endometrium and endometriosis and are believed to play a critical role in the establishment of new implants. The most prominently studied of these factors is VEGF, which is responsible for inducing early vascular growth. This molecule has been noted in endometriosis lesions,[35] endometriomas,[36] and the peritoneal fluid[37,38] of endometriosis patients, although in the latter case it is unclear whether levels are the same as or increased over those in controls. In any event, one potential therapeutic step would be to attempt inhibition of these new vascular structures as a way of deterring the development of endometriosis. This has been performed in the mouse model, where several angiogenic inhibitors (endostatin, TNP-470, celecoxib, and rosiglitazone) reduced the number and size of lesions.[39] No human trials have yet been conducted with these or similar agents.

Matrix Metalloproteinase Inhibitors

Increased matrix metalloproteinase (MMP) activity has been described in endometriosis and is believed to be integral in the ability of endometrium to invade tissue by breaking down extracellular matrix proteins. Inhibition of these enzymes might be effective in inhibiting the development of endometriosis. Only one study has been conducted to date: the MMP inhibitor ONO-4817 was used in the mouse model to deter the development of experimental adenomyosis.[40] The value and practicality of this approach in endometriosis remain to be tested.

Pentoxifylline

Pentoxifylline is a multisite immunomodulating drug. It inhibits phagocytosis and generation of toxic oxygen species and proteolytic enzymes by macrophages and granulocytes, stifles production of TNF-α, and reduces the inflammatory action of TNF-α and interleukin-1 on granulocytes.[41,42] Thus, this medication influences both the production of inflammatory mediators and the responsiveness of immunocompetent cells to inflammatory stimuli. Given the many immunologic abnormalities described in endometriosis, this medication has some rationale in an attempt to correct immune dysfunction. As it is not an inhibitor of ovulation, pentoxifylline has an advantage over ovulation suppressors when attempting to treat endometriosis-associated infertility: it can be administered throughout the time period of attempting conception. Doses have ranged from 400 to 1200 mg daily. The drug is extremely well tolerated, with the major adverse effects being gastric discomfort and dizziness; both are seen in few patients utilizing the recommended dose, and neither has been shown to occur more often in treated patients than placebo controls when giving commercial preparations of the drug.[43]

RESULTS OF MEDICAL TREATMENT

Types of Treatment Trials

Although many studies have been published regarding the medical treatment of endometriosis, not all are of equal importance. A hierarchy of clinical trial design exists that enables the discerning reader to determine which studies should be relied upon most heavily for validity and applicability.[44] These study designs and their place in the hierarchy are listed in Table 1.

Uncontrolled trials have limited value other than to suggest hypotheses to be tested by more rigorous designs. The same is true for historically controlled studies and concurrently controlled nonrandomized trials, each of which introduces significant biases into the results. The "gold standard" today is the randomized clinical trial (RCT), in which subjects are randomly allocated to one of several treatment groups, often in a blinded manner such that the assignment is unknown to the patient or physician until the conclusion of the trial. This design is the least biased of all approaches and results in the most reliable conclusions.

Table 1 Hierarchy of Evidence from Clinical Studies

1. Meta-analysis or large randomized clinical trial
2. Small randomized clinical trial
3. Nonrandomized, concurrently controlled trial
4. Historically controlled trial
5. Case-control study or cohort study
6. Time-series study or anecdotal case reports
7. Expert opinion

Unfortunately, many RCTs are too small to reach a negative conclusion with any degree of confidence. The results of RCTs may also differ from one another because of slight differences in study design, different patient populations, or even as a result of chance events. For these reasons, when multiple randomized trials exist they can often be combined into a single evaluation called a meta-analysis.[45] The meta-analysis allows us to gain a single, best answer to a question with a higher level of confidence than is usually possible with individual studies. However, it is important to keep in mind that a meta-analysis is only as good as the studies included in it; if poor-quality trials are placed into a meta-analysis, the resulting conclusions are as tenuous as those of the component studies.

Assessing Efficacy

The value of a particular medical treatment of endometriosis will vary depending upon the therapeutic goal of the intervention. With regard to endometriosis, there are three outcomes that can be assessed to determine drug efficacy: the anatomic manifestations of the disease, pain symptomatology, and fertility status.

The anatomic manifestations of endometriosis, implants and adhesions, can be assessed before and after therapy to determine whether an intervention is of value. However, such a simple comparison makes two assumptions. First, it is assumed that endometriosis is an invariably progressive disease, never to regress on its own; this is unfortunately incorrect as the disease has, in fact, been noted to regress in both baboonsand humans.[46,47] Second, the comparison presupposed that once regression has occurred via medical therapy, it is stable. This, too, is not the case, as implant and adhesion regrowth are both time-dependent phenomena. Thus, to address adequately the effect of a medical treatment upon endometriosis lesions, a proper control group for comparison is needed, with longitudinal follow-up.

A second outcome of interest is the effect upon pain. The first requirement of quality pain evaluation is a valid method of assessing pain.[48] A second necessity in pain research is longitudinal evaluation, as pain recurrence is a time-dependent phenomenon. Finally, to determine the efficacy of a drug in relieving pain, a large placebo effect must be accounted for. This phenomenon of relief by inactive drug may occur in as many as 55% of women with endometriosis-associated pain.[49] Thus, placebo-controlled trials are needed to determine absolute efficacy; comparative studies between drugs will allow determination of relative efficacy.

The final outcome of interest is fertility enhancement. Unfortunately, it is rare that the woman with endometriosis-associated infertility has absolute infertility due to the disease, as is the case with bilateral tubal blockage or azoospermia. Instead, most women suffering from endometriosis-associated infertility have a relative reduction in fecundity.[47] Thus, they are able to conceive, albeit at a slower rate. To demonstrate improved fertility status after intervention, a comparison group of untreated women is clearly needed. Finally, as fertility is time dependent, longitudinal assessment is again critical.

From the preceding discussion, it is clear that optimal trials are properly controlled and randomized. In addition, it is important to have studies that have lengthy follow-up so that we can determine the long-term course after treatment. Studies such as these will be primarily relied upon in the subsequent discussion.

Medical Treatment of Endometriosis Implants

The effect of medications on implant volume, number, and extensiveness has been examined for a number of drugs in a number of ways. Many are poorly controlled or uncontrolled investigations, and often the observation searching for effect is carried out during administration of the drug itself. Thus, what occurs after drug discontinuation is often a mystery.

An effect of danazol upon endometriotic implants has been consistently observed. Uncontrolled trials have demonstrated implant resolution in the vast majority of treated patients.[50,51] Additional studies have shown a mean decrease of 61 to 89% of implant volume[52,53] and a 43% decrease in the classification score.[54] A single placebo-controlled RCT examined the effect upon implants 6 months following completion of drug therapy, with resolution of implants in 18% of the placebo group and 60% of the danazol treatment group.[55]

Although progestogens clearly affect ectopic endometrium, there is limited information on the histologic effect upon endometriosis. In the rhesus monkey, levonorgestrel has been shown to decrease lesion size. In the human, a single randomized prospective trial demonstrated that MPA at 100 mg daily for 6 months produced complete resolution of implants in 50% of patients and partial resolution in 13%, whereas corresponding figures for placebo were 12% and 6%, respectively.[55]

Several randomized trials have assessed the ability of gestrinone to decrease anatomic endometriosis. The drug has been shown to lower the amount of disease comparably to danazol,[56] and doses as low as 1.25 mg twice weekly can accomplish this.[57,58]

GnRH agonists have been shown in numerous studies to decrease the classification score of endometriosis in patients receiving the drug; similar decreases were seen with the complete American Fertility Society (AFS) classification as well as a modified scoring system that excluded points for adhesions.[59,60] Thus, the effect is limited to causing a lessening of implant volume. In comparative trials, the decrease in AFS score is comparable to that seen with danazol treatment.[61] No study has evaluated the lingering effect of GnRH on implants after discontinuation of the drug, however. GnRH agonist plus add-back therapy has also been shown to decrease the AFS classification score and to a degree similar to that seen with GnRH agonist alone.[62]

Currently, no published data exist for other forms of medical treatment.

Medical Treatment of Endometriosis-Associated Pain

Pain relief has been demonstrated with danazol, with 84 to 92% of women responding.[63] A placebo-controlled RCT proved that danazol reduced pain significantly better than no treatment for up to 6 months following discontinuation of the drug.[55] No good data exist for longer follow-up periods. There is evidence suggesting that the median time to pain recurrence following discontinuation of the medication is 6.1 months.[64]

Few randomized trials exist to evaluate the effects of progestational agents on endometriosis-associated pain. Telimaa and colleagues[55] evaluated the effect of MPA, 100 mg/day for 6 months. The medication produced a significant and substantial improvement in pain scores while patients received the drug as well as up to 6 months following discontinuation.[55] In fact, the relative attributable experimental effect (percent decrease in pain severity attributable solely to treatment) was 50 to 74% at the conclusion of follow-up. Randomized comparative trials suggest that medroxyprogesterone is comparable in efficacy to danazol, although lynestrenol performed less well than a GnRH agonist for all aspects of endometriosis-associated pain.[65]

Numerous uncontrolled trials have evaluated pain relief with oral contraceptives, generally demonstrating improvement in 75 to 89%.[11] An RCT compared cyclic low-dose oral contraceptives with a GnRH agonist and found no substantial difference in the degree of relief afforded women by the two drugs except that the GnRH agonist provided greater relief of dysmenorrhea.[66] An

uncontrolled trial of continuous OCPs following failure of cyclic therapy suggested that this regimen may be superior, as 80% responded with pain relief.[67] However, no RCTs have as yet assessed continuous administration.

The effectiveness of GnRH agonists in the treatment of endometriosis-associated pain has been demonstrated in both placebo-controlled and comparative randomized trials. The one placebo-controlled study available demonstrated greater effectiveness of the drug at 3 months, at which time those in the placebo group still suffering from pain were allowed to opt out of the study.[68] In comparative trials, GnRH agonists and danazol were equally effective in relieving pain.[61,69–83] Oral contraceptives have also been compared with GnRH agonists: in a study of 57 women designed to have 80% power to detect a 35% difference in effect, cyclic oral contraceptive treatment was significantly less effective than GnRH agonist treatment for relief of dysmenorrhea, nearly as effective for relief of dyspareunia (statistically significantly different using one of two rating scales but of questionable clinical importance), and equally efficacious in relieving nonspecific pelvic pain.[66]

Whereas the preceding studies randomly assigned patients for initial therapy of endometriosis-associated pain, one study has examined the value of GnRH agonist in patients failing primary therapy. Ling[84] treated women who did not obtain relief with OCPs with either GnRH agonist or placebo. Those treated with active drug responded significantly better than those given placebo, with more than 80% experiencing pain relief in 3 months (Fig. 1). Of interest is the fact that the therapy seemed to be beneficial whether or not endometriosis was seen at laparoscopy.

Several trials have addressed the efficacy of combined add-back therapy and GnRH agonist treatment during 6-month treatment periods.[85–90] In general, pain was relieved as effectively with the combination as with GnRH agonist alone, and add-back therapy significantly reduced the side effects of the GnRH agonist. The results were similar in three longer trials of approximately 1 year duration.[62,91,92] It seems clear that add-back therapy can be added to GnRH agonist treatment without loss of efficacy but with a substantial amelioration of hypoestrogenic symptoms (Fig. 2). This seems to be the case even when the add-back therapy is begun during the first month of treatment, suggesting that an "add-back free" interval at the beginning of a treatment cycle is unnecessary.[90]

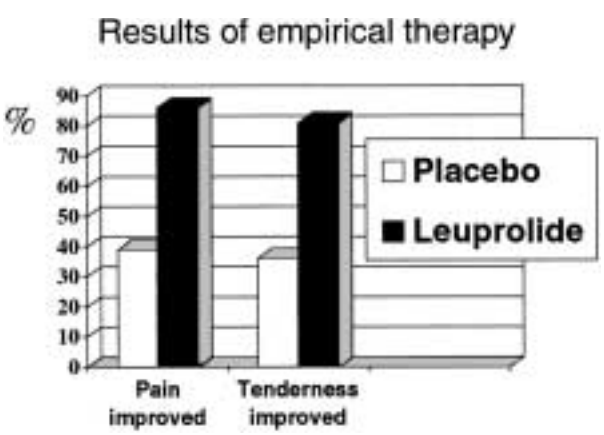

Figure 1 Subjective and objective pain relief with empirical treatment of GnRH agonist for presumed endometriosis following failure of other medical therapy.

Although not approved for use in the United States, gestrinone has been studied extensively. Comparative trials show gestrinone to be roughly equivalent in pain relief to danazol[56] and GnRH agonists.[93] One study has even shown gestrinone to be slightly more efficacious than GnRH agonist for relief of dysmenorrhea 6 months after discontinuation of medication.[93]

Given the preceding data, a number of conclusions can be reached regarding treatment of endometriosis symptoms with medical therapy. It appears that most established medical treatments are effective for the primary treatment of endometriosis-associated pain, and all also seem to be roughly equivalent. Thus, for initial treatment the choice should probably be based on the cost and side-effect profile of the drug being considered. However, only GnRH agonists have been proved effective after the failure of a prior medical hormonal therapy. It remains to be seen what the value is for the newer, investigational therapies; the answers will await upcoming efficacy and comparative trials.

Medical Treatment of Endometriosis-Associated Infertility

Most of the established medical therapies used to treat endometriosis have been applied to the problem of subfertility in women with endometriosis. These medications inhibit ovulation and thus are used to treat the disease for a period of time prior to allowing an attempt at conception. Five randomized trials with six treatment arms have compared one of these medical treatments directed at endometriosis with placebo or no treatment with fertility as the outcome measure[94–98] (Table 2). Another eight RCTs compared danazol with a second medication. The latter trials have been summarized by a meta-analysis by Hughes et al.[99] Clearly, no increase in fertility can be demonstrated with these medications when compared with expectant management; nor has any medication proved superior to danazol in this regard.

Although some studies attempting to assess the absolute efficiency of drug therapy for endometriosis-associated infertility were placebo controlled, others simply compared medication with no treatment. For the latter study design, follow-up of the patient was begun at the conclusion of therapy; thus, those receiving no treatment began attempting to conceive immediately after the

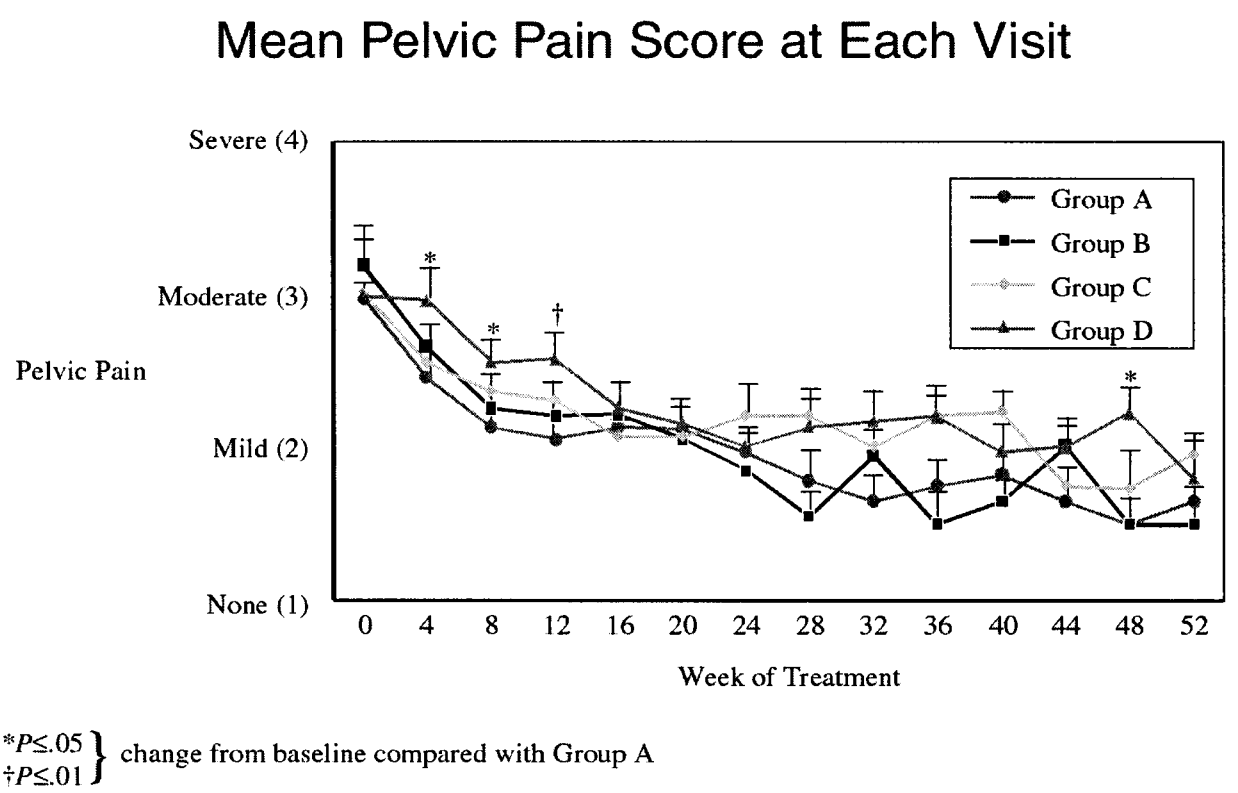

Figure 2 Pain relief with GnRH agonist with and without add-back therapy. Group 1, GnRH agonist alone; group 2, GnRH agonist plus norethindrone; group 3, GnRH agonist plus low-dose conjugated estrogen/norethindrone; group 4, GnRH agonist plus high-dose conjugated estrogen/norethindrone. (Based on data from Hornstein et al.[91])

diagnostic laparoscopy, whereas those receiving drug therapy were not allowed attempted conception until after the medication course was completed (generally 6 months). These studies were analyzed as if the time began at the conclusion of "treatment," but for the patient the clock begins ticking at the time of diagnostic laparoscopy. The real question is not who becomes pregnant faster after therapy is completed but rather who becomes pregnant faster from the time of diagnosis.

If we reanalyze the preceding data, with follow-up proceeding from the time of diagnosis instead of conclusion of treatment, a different image emerges (Table 3). Now, suppressive medical therapy proves significantly detrimental to fertility. In essence, the interval spent on medical therapy has been wasted time, merely serving to prolong the infertility in a number of couples. Thus, traditional medical therapy for endometriosis has not proved to be of value and in fact may be counterproductive to the subfertile patient.

This is not to suggest that traditional medical therapy is incapable of playing a role in the treatment of the infertile couple with endometriosis. It is quite possible that a subgroup of infertile women exist who could be helped with drug therapy. However, this subgroup is thus

Table 2 Meta-Analysis of Medical Therapy for Endometriosis-Associated Infertility

Study	Medical Treatment	Placebo or No Treatment	Relative Risk	95% Confidence Limits
Bayer[94]	11/37	17/36	0.63	0.32–1.22
Fedele[97]	17/35	17/36	1.03	0.60–1.76
Telimaa[95]	13/35	6/14	0.87	0.41–2.25
Thomas[98]	5/20	4/17	1.06	0.28–4.29
Harrison[96]	0/50	3/50	0.00	0.00–2.18
Total	46/177	47/153	0.85	0.59–1.22

Table 3 Meta-Analysis of Medical Therapy for Endometriosis-Associated Infertility: Adjustment for Follow-up from Time of Diagnosis

Study	Medical Treatment	Placebo or No Treatment	Relative Risk	95% Confidence Limits
Bayer[94]	11/37	17/36	0.63	0.32–1.22
Fedele[97]	10/35	13/36	0.79	0.36–1.68
Telimaa[95]	4/35	5/14	0.32	0.08–1.24
Thomas[98]	4/20	4/17	0.85	0.20–3.69
Harrison[96]	0/50	3/50	0.00	0.00–2.18
Total	29/177	42/153	0.60	0.38–0.93

far unidentified; advocates should focus future trials upon somehow stratifying endometriosis patients and then randomizing to drug versus no treatment. Until that time, it is clear that these medications play no role in the treatment of endometriosis-associated infertility.

Among the experimental treatments for endometriosis, only pentoxifylline has been investigated as a treatment for endometriosis-associated infertility. This drug has the advantage of not inhibiting ovulation and thus can be utilized without delay of attempted conception. A single placebo-controlled RCT with 60 patients resulted in a 12-month pregnancy rate of 31% with pentoxifylline and 18.5% with placebo, a difference not statistically significant but intriguing nonetheless.[100] It is hoped that additional, larger trials will further investigate this approach to help clarify the value of this and similar drugs.

Medical Therapy Following Surgery

Frequently, clinicians have used drugs in combination with surgical treatment of the disease. When this approach is utilized, the medical therapy may be administered either preoperatively or postoperatively.

Only one randomized trial has evaluated the value of preoperative hormonal therapy.[101] In this study, women with advanced endometriosis were either treated for 3 months with a GnRH agonist prior to surgery or with surgery alone. Surgery was noted to be easier (but not statistically significantly easier) by the surgeon, but surgical outcome was not assessed in terms of symptomatic relief.

Numerous RCTs have examined the issue of postoperative medical therapy as an effective adjunct for pain. Danazol was found not to enhance the results of surgery when administered for only 3 months,[102] but 6 months of postoperative administration reduced pain versus placebo for at least 6 months following discontinuation of the drug.[103] High-dose medroxyprogesterone behaved similarly.[103] Three RCTs have examined the use of postoperative GnRH agonists: 3 months of treatment was ineffective at enhancing pain relief,[104] but 6 months of postoperative therapy significantly reduced pain scores and delayed recurrence of pain[105,106] (Fig. 3). The use of oral contraceptives for 6 months following surgery has been shown ineffective in improving the results of surgery.[107] Finally, an RCT compared postoperative use of a levonorgestrel-containing intrauterine device (IUD) versus surgery alone and found that all forms of pelvic pain were significantly reduced postoperatively by the addition of the IUD.[108]

One RCT has examined the use of a single postoperative medical therapy versus two sequential medical treatments following surgery. Morgante and colleagues[109] compared the use of 6 months of postoperative GnRH agonist therapy with 6 months of GnRH agonist followed by 6 months of danazol, 100 mg/day. Twelve months following surgery (at the conclusion of danazol for one group and after 6 months of no treatment for the other), there was significantly less pain in those treated with the two sequential medical treatments.

Three studies have investigated the use of postoperative medical therapy for fertility enhancement, utilizing GnRH agonist[105,106] and raloxifene,[110] a selective estrogen receptor modulator. None have demonstrated any enhancement of fertility in women with endometriosis utilizing this approach.

Although these studies suggest that postoperative medical therapy is of value when used for 6 months or more, a word of caution must be interjected. As is the case with all surgical trials, the degree of surgical skill and the technique used may be critical in determining the results. At least one retrospective trial has indicated that excision of endometriosis results in greater pain re-

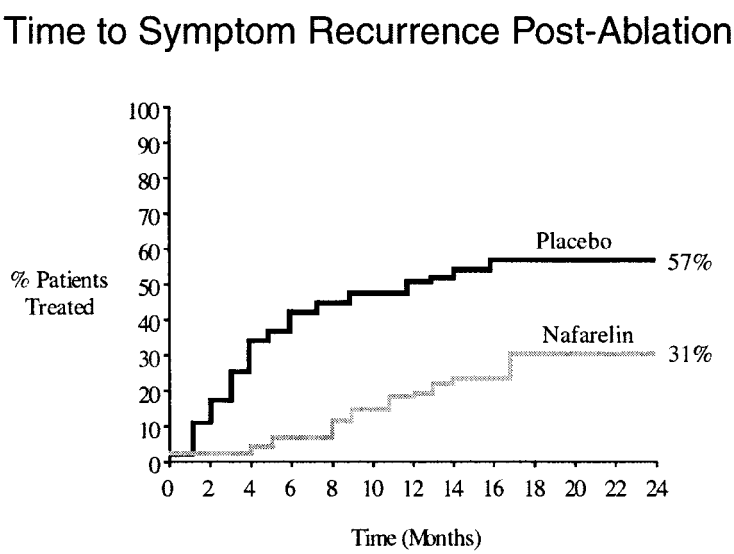

Figure 3 Rate of recurrence of pelvic pain following treatment with surgery alone versus surgery followed by GnRH agonist therapy. (Based on data from Hornstein et al.[105])

lief than ablation of lesions (C. Winkel, unpublished data), yet ablation is generally the treatment of choice with these studies. Furthermore, we have no way of ascertaining the degree of surgical skill that was applied in the surgical treatment of these patients. Additional high-quality studies are needed in a variety of settings by a larger number of surgeons to examine this issue further and confirm the preceding results.

CONCLUSIONS

The use of medical therapy in the treatment of endometriosis has a long and colorful history, with a wide variety of medications having been tried. For decades we had little in the way of scientific information to guide us, but today the proliferation of RCTs in our literature provides the discerning clinician with excellent clues as to how best to approach the treatment of symptomatic disease. One clear deficiency in the literature, however, is the lack of a direct comparison between medical and surgical therapy in the treatment of endometriosis-associated pain. Although several randomized trials have been attempted, none has ever been completed. Data from placebo- and sham-controlled studies suggest similar success rates, but these investigations have been carried out in different patient populations under different conditions. Until an RCT comparing medicine and surgery is carried out, the relative merits of each are purely speculative.

Nonetheless, what is clear from the preceding data is that medical therapy can be of value in the treatment of endometriosis, particularly in regard to pain symptoms. Furthermore, with a wide variety of investigational medications in the pipeline, it is likely that the role of medication for this disease will expand in the future. As this occurs and our treatment options expand, we are likely to see an era of improved efficacy with fewer side effects for more patients, a situation clearly advantageous to the many women suffering from endometriosis.

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