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Endometriosis: Traditional Perspectives, Current Evidence and Future Possibilities

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ABSTRACT: Endometriosis is a disease that is wide-ranging in location and highly varied in clinical presentation, and of probably complex etiology. Since convincing studies on this condition are few, many physicians maintain a traditional perspective in management and treatment. There is new evidence, though, on some aspects of endometriosis. Therefore, this review of many of the better studies outlines treatments that are aimed at pain and/or infertility, plus an assessment of the outcomes obtained. The methods covered are symptomatic treatment; ovarian suppression; surgery; combined ovarian suppression and surgery; ovarian hyperstimulation; assisted reproductive technology; and comprehensive management, including counseling. *Int J Fertil* 46(3):151–168, 2001

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INTRODUCTION

ENDOMETRIOSIS IS AN ENIGMATIC disease affecting about 7% of reproductive-age women—approximately 6 million Americans. Most of these women do not know that they have endometriosis, although many suffer significant pathology, ranging from pelvic pain to infertility to ovarian tumors. Many clinicians retain traditional perspectives about endometriosis, because good clinical studies have been limited in number, resulting in a surfeit of opinion and paucity of facts. However, current concepts, increasingly based on sound data, have resulted in a more evidence-based approach to treatment. Importantly, basic science initiatives should create better understanding and improved future management of this complex medical condition [1,2].

MANAGEMENT OPTIONS

Assessment of the reproductive goals of the endometriosis patient is necessary in order to determine the best treatment. Treatment objectives are to remove or destroy endometrial implants, relieve symptoms, maintain or restore normal anatomy, maintain or improve fertility, and avoid or delay recurrence of the disease.

Reflective of its elusive pathophysiology, treatment options for endometriosis are varied and numerous and can be divided into symptomatic treatment, including analgesia with nonsteroidal anti-inflammatory drugs (NSAIDs) or low-dose intermittent narcotics, ovarian suppression, surgical treatment, combinations of the latter two, ovarian stimulation and/or the assisted reproductive technologies. Since some of the treatments prevent pregnancy and others are specifically directed at achieving conception, thorough knowledge of the patient's objectives is essential.

Symptomatic Treatment

"No treatment" includes expectant management, and/or limited use of analgesics and NSAIDs that do not treat the disease but alleviate symptoms. These may be especially helpful for women with

dysmenorrhea associated with endometriosis. NSAIDs are frequently the first-line treatment in women with pain who have not yet been proven to have the disease: failure to respond requires more extensive evaluation and treatment. Patients should initiate NSAIDs immediately upon feeling any premenstrual symptoms and continue medication for three days. It is important to avoid addiction to analgesics and NSAIDs, and patients requiring more than usual dosing need careful pain management.

Ovarian Suppression

Ovarian suppression can be accomplished with oral contraceptives (OCs), progestins, danazol, GnRH agonists or GnRH antagonists. Oral contraceptives can be given cyclically, but many patients do better with continuous active-ingredient tablets for 3 months, followed by withdrawal, and then repetition. Monophasic OCs are superior to triphasic OCs for this indication. The best dosage to begin is usually 35 μg of ethinyl estradiol, but this can be decreased if the patient is symptomatic with headaches, or increased in case of breakthrough bleeding. Norethindrone 0.35 to 0.5 mg daily may be added if the patient is still symptomatic with bleeding. Transdermal estradiol (Estraderm) 0.05 mg or 0.1 mg twice weekly may also be used if this is better tolerated. Treatment lasts 3 to 6 months [3].

The most commonly used progestin is medroxyprogesterone acetate (Provera) 30 mg/day, or up to 100 mg/day in some studies. Side effects include breakthrough bleeding, mastalgia, bloating, weight gain, nausea, fluid retention and depression. Fortunately, all resolve after discontinuation of the medication. Progestins alone may be useful in a few women who cannot tolerate oral contraceptives. Treatment is inexpensive [3].

Danazol (Danocrine) (200–400 mg twice a day) is an isoxazole derivative of 17α-ethinyltestosterone, which functions by suppressing follicle-stimulating hormone (FSH) and luteinizing hormone (LH) from the pituitary gland, inhibiting steroidogenesis enzymes and increasing serum free testosterone, resulting in a hypoestrogenic state. Additionally, there is a direct effect on endometrial-like tissue and an immunologic component to action which may have a salutary effect on the endometriosis process. Doses of danocrine as low as 50 mg/day have sometimes been effective. Most concerning to the patient are increased hair growth, mood changes, depression, and an adverse effect upon serum lipid profiles. Moreover, the increased serum free testosterone produces other androgenic side effects, including weight gain, vasomotor instability (hot flashes), muscle cramps, acne, edema, hirsutism, reduced breast size, vaginitis, and sweating. Danazol is contraindicated during pregnancy and lactation, and in women with undiagnosed abnormal genital bleeding or markedly impaired hepatic, renal, or cardiac function. These pharmacologic effects are reversed within 2 months of discontinuing treatment, but uncommon, potentially irreversible side effects include voice change and clitoral hypertrophy.

Gestrinone (ethylnorgestrienone) is a 19-nortestosterone derivative that acts as an androgen receptor agonist and a progesterone receptor agonist/antagonist, the net result being amenorrhea. The potential side effects are androgenic and antiestrogenic, similar to those of danazol; they tend to be mild and transient, and less frequent than with danazol. While most are reversible, some such as voice change and clitoral hypertrophy are sometimes irreversible. Gestrinone is typically administered in oral doses of 2.5 mg two or three times a week. Symptomatic relief usually occurs within 2 months.

GnRH agonists are synthetic decapeptides. Nafarelin acetate (Synarel) (200 μg nasal spray used twice a day) is a superactive, hydrophobic stimulatory analog of GnRH that is 200 times as potent as naturally occurring GnRH, and is delivered in a metered nasal spray pump [4]. Leuprolide acetate (Lupron Depot) is usually given as a single monthly 3.75-mg intramuscular injection, or sometimes a single 3-month injection [5]. The GnRH agonists result in an initial stimulation of the pituitary gland, but after 7 to 14 days hypoestrogenemia (estradiol less than 40 pg/mL) ensues with resultant amenorrhea, which permits regression of endometriosis and relief of symptoms. The GnRH agonists do not have any known direct effects on the ovary. Treatment costs approximately $3,000 for 6 months.

Side effects include hot flashes in about 90% of patients, decreased libido, vaginal dryness, mastalgia, joint stiffness, skin changes, headaches, fatigue, emotional lability, and insomnia. Cardiovascular and liver enzyme markers show favorable changes relative to danazol. The major concern with GnRH

agonists is the loss of bone density, about 3–8%, which occurs over 6 months of drug therapy, with a 2–3% loss persisting about 1 year following treatment. The FDA and others' consensus is that this is not clinically significant in women who have no evidence of bone disease, and it is not generally necessary to perform an evaluation of bone density before initiating treatment. While only one 6-month course of GnRH agonist is FDA approved, studies have shown that 3 months of treatment, both initially and from subsequent retreatment if symptoms recur, is as effective as 6 months of treatment, and is associated with less bone loss. Patients should generally undergo dual-photon absorptiometry (DPX) and have normal bone density before GnRH agonist retreatment, and should be fully informed of the potential risks. Hot flashes can be effectively managed with norethindrone (Micronor) 2.5 mg per day. Higher doses of norethindrone may provide some protection against bone loss, but have an unfavorable side effect profile for liver and cardiovascular systems, and patients are often highly symptomatic. Low doses of estrogen (Premarin 0.6 mg per day) have also been used as "add-back" therapy to reduce bone loss, and show some promise. More recently, add-back therapy for 6 to 12 months with norethindrone 2.5 mg to 5 mg and alendronate 10 mg per day has been suggested, along with calcium 1,000 mg per day. However, the long-term efficacy of such add-back therapy and its effect on the therapeutic efficacy of the GnRH agonist is still being evaluated. Some data show that even add-back therapy does not protect against bone loss when GnRH agonists are used for long periods. Symptoms that return following GnRH agonist treatment may also be treated with oral contraceptives, danazol, and/or surgery.

A new therapeutic class of drugs, the gonadotropin releasing hormone (GnRH) antagonists, have significant physiologic differences from the widely used GnRH agonists. While the agonists cause an initial flare or stimulatory response with subsequent down-regulation and inhibition, the antagonists cause prompt competitive inhibition of native GnRH actions. The antagonists may therefore be given later in the follicular phase when suppression of luteinizing hormone (LH) is required, allowing endogenous LH and FSH to be present early in the cycle. Gonadotropin releasing hormone antagonists (GnRH antagonists) such as Antagon are just being introduced into clinical care. Their potential advantages and disadvantages for endometriosis treatment have yet to be determined, but their immediate down-regulation effect and resulting hypoestrogenemia may be beneficial in some endometriosis pain patients.

Other medications which have been used or considered but are now largely abandoned include estrogen, methyltestosterone, tamoxifen, clomiphene, pentoxifylline and RU486. In the future, selective estrogen-receptor modulators (SERMs), next-generation progesterone receptor antagonists, and aromatase inhibitors might prove useful [6].

Surgery

Most patients undergoing endometriosis surgery wish to have disease alone removed and retain functionality of their pelvic organs. For some, however, hysterectomy and/or oophorectomy is a reasonable approach if other treatments have failed and/or other indications for extirpation exist. At the time of surgery all lesions should be treated regardless of whether or not organ extirpation is performed. Elimination of endometrial implants may be achieved by laser ablation, sharp resection, or electrosurgery. The excellent precision of the CO_2 laser allows the surgeon to create tissue injury at a precise and identifiable localized area, but with poor coagulating ability. The KTP532 and argon lasers are less precise than the CO_2 laser, but have better coagulating properties. The Nd:YAG laser has very good coagulation properties but poor precision, and can cause large-volume thermal injury that is mostly invisible to the operator. Sharp resection is highly effective, with a low risk of inadequate treatment but is prone to increased bleeding. Unipolar electrosurgery, while effective, carries the risk of deeper tissue damage. Bipolar electrosurgery, like the laser, can eradicate small lesions. With electrosurgical desiccation, however, the precise extent of tissue destruction cannot be determined and thus there is a risk of inadequate treatment. Treatment outcomes using the CO_2 laser, KTP532 laser, argon laser, and electrosurgery during laparoscopy appear to be comparable. The value of any energy source used surgically lies primarily in the skill of the surgeon using it.

Prior to the advent of laparoscopy, laparotomy was the treatment of choice for advanced endometriosis. The main advantage over laparoscopy is the ability of the surgeon to palpate different structures directly. Laparotomy may also

be preferred in cases requiring removal of large endometriomas or in cases deemed too complex for laparoscopic treatment, such as bowel resection. Disadvantages include greater tissue trauma, which may result in more adhesion formation, exposure of abdominal contents to dry air and foreign bodies, and longer recovery time.

Diagnostic laparoscopy provides a relatively safe and simple method of diagnosing endometriosis [7,8]. When appropriate, operative laparoscopy enables treatment to be initiated and possibly completed at the same time. Surgical therapy is usually conservative, consisting of excision, laser vaporization, or electrosurgical fulguration of endometriosis. In cases of advanced disease, radical surgery comprising hysterectomy and/or bilateral salpingo-oophorectomy may be required. Laparoscopic treatment of endometriosis requires a surgeon who is familiar with the pathophysiology of endometriosis, and can integrate this knowledge with surgical judgment and technique. Medical and surgical treatment modalities sometimes produce similar results, but surgical treatment completed at the time of diagnosis has a distinct advantage over medical therapy because of decreased time, cost, and side effects. The patient can also be spared a second operation (laparotomy) if operative laparoscopy can be performed at the time of diagnosis. Operative laparoscopy offers several advantages over laparotomy, primarily because of better visualization, less tissue trauma, and much shorter recovery time. However, tactile sense is less than that which can be obtained digitally at laparotomy. It is more important to give the patient the best operation possible in the particular surgeon's hands than to compromise it by performing a poor operation at laparoscopy. The guiding surgical principle is complete removal of all endometriosis lesions, fibrosis, and adhesions, including those requiring deep dissection. Surgeons should perform diagnostic laparoscopy only if they are prepared to treat surgically all lesions found at the laparoscopy. If the surgeon does not have the skills or facilities to do this, the patient should be referred. Biopsy of suspected lesions should be performed to confirm the diagnosis.

There is often hesitation to perform operative laparoscopy for ovarian endometriomas in the event that there may be co-existing carcinoma. However, most adnexal masses are benign, and many experienced laparoscopists believe that by strictly adhering to established guidelines patients will not be placed at greater, if any, risk by performing an operative laparoscopy. Preoperative bowel preparation is advised in many cases.

In treating ovarian endometriomas laparotomy has been the traditional approach due to the ineffectiveness of medical treatment [9]. Most clinicians believe ovarian endometriomas require surgical extirpation with complete removal of the cyst wall and occasional reconstitution of the ovary with a suture. Other approaches have been suggested, including no treatment, hormonal suppression, drainage only, coagulation, and combined treatment with hormonal suppression and staged surgery. Failure to treat adequately can result in chronic symptoms. Drainage is uncommonly successful, but may occasionally be indicated in patients with smaller endometriomas who have had multiple operations. Following cystectomy, normal ovarian function appears to be retained. Some data suggest that multiple ovarian operations will result in reduced ovarian function. The recurrence rate of resected endometriomas is less than 10%, with an incidence of de novo adhesion formation of 20% and partial dense adhesion recurrence of 80%.

Adhesions can disrupt normal anatomic relationships and restrict the mobility and distensibility of organs, potentially resulting in pain. A correlation, however, between the extent or location of adhesions and the severity of pain has yet to be demonstrated. Despite the uncertainty in the relationship between adhesions and pain, lysis or removal of adhesions is reasonable in the setting of endometriosis-associated pain, especially when the locations of adhesions and pain seem related.

Laparoscopic uterosacral nerve ablation (LUNA) is a procedure that interrupts the sensory nerve fibers and associated ganglia as they exit the uterus. It has been used for relief of endometriosis-associated pain. In the treatment of dysmenorrhea, pain relief after 3 months has been observed in over 80% of women receiving treatment, compared with no relief in untreated women. Symptoms recur after 1 year, however, in approximately half of the women. LUNA is a reasonable consideration when the uterosacral ligaments are involved with endometriosis, or when patients with central chronic pain are refractory to other therapies.

Presacral neurectomy is another procedure used for endometriosis-associated pain that has had variable results. This technique involves interrupting the sympathetic innervation to the uterus at the

level of the superior hypogastric plexus. Conflicting data exist regarding the efficacy of presacral neurectomy in relieving dysmenorrhea, dyspareunia, and pelvic pain. In light of the variable results, technical difficulty and complications of the procedure, presacral neurectomy should be considered only in selected patients with midline dysmenorrhea unresponsive to conservative treatment.

Endometriosis can affect other specific pelvic structures. For tubal endometriosis, CO_2 laser ablation to minimize thermal injury and control depth has been quite effective. Proximal tubal occlusion requires resection followed by anastomosis or cannulization. Bladder endometriosis may be deep, necessitating resection. Ureteral endometriosis can cause anatomic distortion, in which case intraureteral catheters may be helpful in selected cases. The CO_2 laser can provide precise and safe ureterolysis, although resection–anastomosis may be necessary here, too, as a consequence of scarring and fibrosis. Invasive bowel endometriosis may require bowel resection, in which case a coordinated approach by general and reproductive surgeons is necessary.

Combined Ovarian Suppression and Surgery

Laparoscopic treatment of endometriosis may sometimes be combined with ovarian suppression. The purpose of combined treatment is to improve treatment success or facilitate surgical procedures, for example, by preventing functional ovarian cysts so that they are not present or confused with endometriosis. Metastatic or extensive superficial disease is suppressed and becomes atrophic. The reduced vascularity in the pelvis may result in reduced inflammation and postoperative adhesions, although the latter has not been proven. There may be a slight reduction in endometrioma size. Other uses of GnRH agonists prior to surgery include reduction of symptoms, increased time for adequate preoperative evaluation, easier scheduling of surgery, and even delay or avoidance of surgery for a woman approaching menopause.

Potential disadvantages of preoperative ovarian suppression include the changed appearance of endometriosis, which might make it more difficult to diagnose; drug cost and side effects; delay of diagnosis; and delay in attempting pregnancy. Postoperative ovarian suppression may be indicated if complete resection of disease has not been accomplished, for treatment of microscopic or metastatic disease, or for treatment of pain. Preoperative or postoperative treatment is usually given for 2 months to 6 months, but 3 months is adequate for most patients. A very successful treatment approach is to use oral contraceptives continuously for 3 months, withdraw for 1 week, and repeat the 3 months of treatment. This cycle can be continued even to menopause or to the time of attempting pregnancy. It is the most cost-effective approach for many patients.

Controlled Ovarian Hyperstimulation

Controlled ovarian hyperstimulation (COH) is the intentional induction of multiple ovulation to increase the number of eggs which are ovulated in an otherwise normally ovulating woman [10]. COH is often carried out with intrauterine insemination (IUI) with prepared sperm. Sperm processing allows the selection of sperm with the most normal morphology and motility and the absence of white cells, and other infectious organisms. Intrauterine insemination avoids cervical problems such as poor mucus, cervical antibodies, and infection.

COH-IUI may be helpful for women with stage I-II endometriosis. Generally, three to six cycles of COH-IUI are clinically appropriate. A maximum number would be six cycles of CC-IUI and six cycles of hMG-IUI in selected patients. Some controversy exists as to the optimal number of inseminations per cycle. The data would generally support one well-timed IUI when an adequate number of sperm is present. Should timing of insemination be difficult to determine, two inseminations two days apart may be helpful and may improve pregnancy rates. In addition, at least 1 million total motile sperm should be available for intrauterine insemination; a number lower than this will result in lower pregnancy rates. Pregnancy rates will increase slightly with 5 million total motile sperm per inseminate, and increase only minimally beyond 5 million total motile sperm per inseminate.

Assisted Reproductive Technologies

The assisted reproductive technologies (ART) refer to procedures such as in vitro fertilization (IVF), gamete intrafallopian transfer (GIFT), zygote intrafallopian transfer (ZIFT), intracytoplasmic

sperm injection (ICSI) and assisted hatching. Results for 1997 from the United States IVF Registry gave a 27.9% delivery rate per retrieval for IVF, a 30.0% delivery rate for GIFT, and a 28.0% rate for ZIFT [11]. GIFT may have a slightly higher success rate than IVF, and may be recommended for women with known normal tubal function when sperm function is normal, and possibly in older women. However, it is not clear whether the apparent increase in GIFT success rates is real or due to other factors, such as patient selection. There is only a slight reduction in the success rate of IVF with increasing numbers of cycles, each cycle after the first having approximately 90% the success rate of the first. An increasing duration of fertility also decreases success rates. Previous pregnancy and live birth increase success rates slightly.

Comprehensive Management Approach

It is critical that physicians recognize the degree to which endometriosis can physically and emotionally disrupt patients' lives, and provide comprehensive understanding and an empathetic management approach [12,13]. Attention to healthy life style with respect to diet, exercise, sleep, and stress reduction through mind–body techniques can be very helpful. Psychological support through information can be obtained from such organizations as the Endometriosis Association, RESOLVE, and the American Society of Reproductive Medicine. Personal or group counseling may also be helpful, especially for the patient with chronic pain. Some patients may seek nontraditional and unproven approaches to treatment, such as acupuncture, herbal medicine, or special diets. Management in these chronic, complex situations should focus on alleviation of symptoms and improved quality of life. A comprehensive evaluation of gastrointestinal, genitourinary, musculoskeletal, neurologic, and psychologic systems may be indicated. Referral to a pain clinic may be helpful for further treatment, including biofeedback strategies, nerve blocks, psychotherapy, or other pain management techniques.

Treatment of reactive depression is often necessary, and often requires a multidisciplinary approach. A comprehensive long-range treatment approach needs to be individualized for each patient. A complete cure can sometimes be achieved only by total hysterectomy and bilateral salpingo-oophorectomy. Patients with chronic pain (as many of these patients have) should be treated with a comprehensive mind–body approach—diet, exercise, sleep, and biofeedback. A focus on a better quality of life as defined by what the patient wants to do, such as whether she gets to school or work every day, is a useful measure of outcome.

TREATMENT OUTCOMES—PAIN, INFERTILITY

Ovarian Suppression

No treatment and/or mild analgesics or NSAIDs may be entirely appropriate for many young patients with minimal symptoms, or for women who have just completed a course of ovarian suppression. Women who remain symptomatic with minimal or mild pain may frequently be successfully treated with cyclic oral contraceptives, and this treatment should be attempted in most women. Cyclic oral contraceptives do not work as well for dysmenorrhea as ovarian suppression regimens that produce amenorrhea, but are nearly as effective for relief of dyspareunia and equally effective for nonspecific pelvic pain.

Placebo-controlled studies have demonstrated that medroxyprogesterone acetate 100 mg/day, danazol 600 mg/day, nafarelin acetate 200 μg twice daily, and leuprolide acetate 3.75 mg/month for 6 months produce significant and substantial improvement in pain scores for 70% to 90% of patients [4,5,14–16]. Six months after discontinuation of treatment about two-thirds of patients experience dysmenorrhea, about half have pelvic pain, and one-third have dyspareunia. Endometriosis recurs annually in 5% to 20% of patients, reaching a cumulative rate as high as 50% at 5 years following completion of conservative therapy, consisting of about 35% for minimal disease and 75% for severe disease. Dysmenorrhea returns with menses and presumably the cyclic release of endometrial prostaglandins [17,18]. Patients with severe disease or large endometriomas tend to have an earlier recurrence. The ASRM staging system has a very limited ability to correlate the extent of endometriosis with the presence, persistence, or recurrence of pelvic pain [19]. Randomized controlled trials have shown that "add-back" therapy in conjunction with GnRH agonists does not affect symptom relief, but medication side effects *are*

diminished. Two studies yielded similar results with longer than 6 months of treatment. Therefore, ovarian suppression therapies are superior to placebo in the treatment of endometriosis-associated pain, and all the medications are approximately equivalent. The decision to use GnRH agonists, danazol, oral contraceptives, or progestins should be based on cost, side effect profile, and individual patient response to any given medication [20–25].

Surgical Treatment

There are limited data from good studies to evaluate the outcome of pain relief following surgery for endometriosis. Laparoscopic and laparotomy treatment appears effective, with approximately 60–90% of patients showing significant clinical improvement following complete resection of disease. Some 60% to 90% should have reasonable symptom relief at 1 year, 50% to 80% at 5 years, and 50% at 10 years if the disease is completely resected. Pain relief is often initially better in patients with more severe disease, but patients with more severe disease are at higher risk of recurrence than those with mild disease. Recurrence rates overall are 10% to 20% per year [26–30].

Deep rectovaginal lesions appear to be correlated with severity of disease, with complete excision offering the best results, 70% having relief postoperatively and a recurrence rate of some pain as high as one-third, but with only 5% having severe symptoms and recurrence at 5 years [31,32].

Adhesions often distort normal anatomic relationships, potentially resulting in restriction of mobility and distensibility of organs and pain. However, a relationship between the extent or location of adhesions and the severity and duration of pain has not been demonstrated [33]. Uncontrolled studies have shown adhesiolysis to result in improved pain symptoms in approximately 85% of patients. Adhesion re-formation occurs in most patients, with the amount of re-formation correlated with the initial adhesion extent, about one-third of mild, two-thirds of severe, and over 90% of extensive adhesions re-forming. Despite this uncertainty regarding the relationship between adhesions and pain, lysis of adhesions appears reasonable in the presence of endometriosis-associated pain, especially when the locations of adhesions and pain correlate [34].

Laparoscopic uterosacral nerve ablation (LUNA) is another procedure used for the treatment of endometriosis-associated pain [35]. In a prospective, randomized, double-blind study of women with intractable dysmenorrhea, pain relief following LUNA was observed in 81% of women after 3 months, compared with no pain relief in women not having LUNA. However, recurrence of pain after 1 year was reported by approximately half of the women. In the presence of minimal to moderate endometriosis, another study showed improvement in pain symptoms following LUNA and ablation of endometriosis in 62% of women, compared with 23% of untreated women. Another study comparing conservative surgery with or without LUNA showed no difference between the groups. Thus, LUNA appears to be reasonable when the uterosacral ligaments are involved with endometriosis, or when patients with central chronic pain are unresponsive to other therapies and are undergoing surgery; but there is no convincing evidence that by itself it reduces pelvic pain.

Presacral neurectomy involves interrupting the sympathetic innervation to the uterus at the level of the superior hypogastric plexus. This technique has had variable results when used to treat endometriosis-associated pain. In a randomized, prospective study, presacral neurectomy effectively relieved midline dysmenorrhea but had variable effects on dyspareunia, lateral pain, and back pain [36]. In another randomized, controlled study, however, no significant difference in the frequency and severity of dysmenorrhea, pelvic pain, and dyspareunia was observed [37]. Due to the variable results and the risk of permanent bowel and/or bladder dysfunction, only selected patients with primarily midline dysmenorrhea unresponsive to conservative treatment should be considered for presacral neurectomy.

Endometriosis-associated pain may be effectively reduced by definitive surgery with hysterectomy and/or salpingo-oophorectomy. This approach would be considered in patients who fail medical and/or conservative surgical treatment and can accept loss of fertility. Alternatively, a definitive surgical approach as the primary option may be considered in women who have completed childbearing and desire this approach. Persistence of symptoms due to adhesions, residual peritoneal lesions, or ovarian remnant syndrome is possible during the course of endometriosis treatment. Pain

relief following hysterectomy will be observed in up to 90% of patients, and elimination of dyspareunia in 66% [38]. Symptoms recur in 15%, and additional surgery is needed in 5% to 10% of patients. If the ovaries are removed, the recurrence rate is about 8% and the reoperation rate about 3–5%. In moderate or severe endometriosis, the risk of recurring pelvic pain has been suggested to be increased up to fivefold if the ovaries are not removed at the time of hysterectomy. Recurrence probably most often relates to the failure to remove deep nodular endometriosis at the time of hysterectomy, and so disease persists rather than recurs.

Properly performed initial surgery appears superior to medical treatment for pain, especially in patients with more severe disease, but not necessarily in patients with chronic pelvic pain and minimal or mild disease, especially once that disease has been initially resected.

Combined Ovarian Suppression and Surgery

Three randomized, placebo-controlled trials have evaluated the use of post-operative medical therapy as a means of providing further pain relief. Studies by Telimaa et al [39] (danazol or medroxyprogesterone) and Hornstein and associates [40] (GnRH-agonist) suggest a benefit this combination approached. The former study demonstrated a relative decrease in pain scores attributable to combination therapy of more than 60% for each drug. The Hornstein study found that combination therapy decreased the number of patients needing retreatment within 2 years from 57% to 31%. However, no significant difference in pain scores was seen between groups. In contrast, Parazzini et al [41] found no difference in the use of three months of GnRH-agonist post-operatively versus surgery alone, with one-year follow-up. These results fail to present a consistent view of the value of combination therapy; clearly, further studies are needed for clarification [42].

Ovarian Endometrioma Treatment

Because of the ineffectiveness of medical treatment in eradicating endometriomas, traditional therapy has required laparotomy. The improvement in laparoscopic technique and technology has allowed the advanced treatment of endometriomas [43]. Ovarian endometriomas have been treated by various surgical techniques. Cyst stripping or ablation, drainage, and wedge excision yield similar results in improving pain symptoms. Pain relief following surgery has been observed in 60% to 100% of patients. The approach of wide excision and drainage has been recommended as an alternative to wedge excision on account of less adhesion formation and a recurrence rate of 23%, similar to cyst stripping and ablation. In other studies, stripping or ablation, perhaps the most widely used techniques, have been associated with even lower endometrioma recurrence rates of less than 10%.

Pregnancy rates following endometriomectomy at laparoscopy or laparotomy are approximately 50% at 2 to 3 years by life-table analysis, and are not dependent on the number or size of endometriomas, but can be affected by the extent of adhesive disease [43]. Following drainage and cystectomy surgery, the ovary appears to retain normal function. Resected endometriomas have been shown to have a recurrence rate of approximately 10%, with an approximately 20% incidence of de novo adhesion formation and an approximately 80% incidence of partial dense adhesion recurrence [44]. Other studies show an ultrasonographic recurrence rate of about 12% and reoperation rate of 8% over 4 years if treated properly. Ultrasonographic demonstration of cyst recurrence was associated with pain recurrence in 73% of cases. One study showed no difference in the long-term recurrence rate of endometriomas after surgical removal and treatment with cyclic monophasic oral contraceptives compared with no treatment, but the recurrence rate by life-table analysis appeared to be lower with use of oral contraceptives.

Infertility Outcomes

Ovarian Suppression. Four randomized trials have compared ovarian suppression with placebo or no treatment, and eight have compared ovarian suppression medications with danazol [45]. All have been summarized in a meta-analysis by Hughes et al [15]. The results of our meta-analysis also provided strong evidence that there was no significant difference in crude pregnancy rates between medical treatment and no treatment (Figure 1) [46]. The combined estimated risk ratio was 0.98, with a 95% confidence interval of 0.81 to 1.18. No

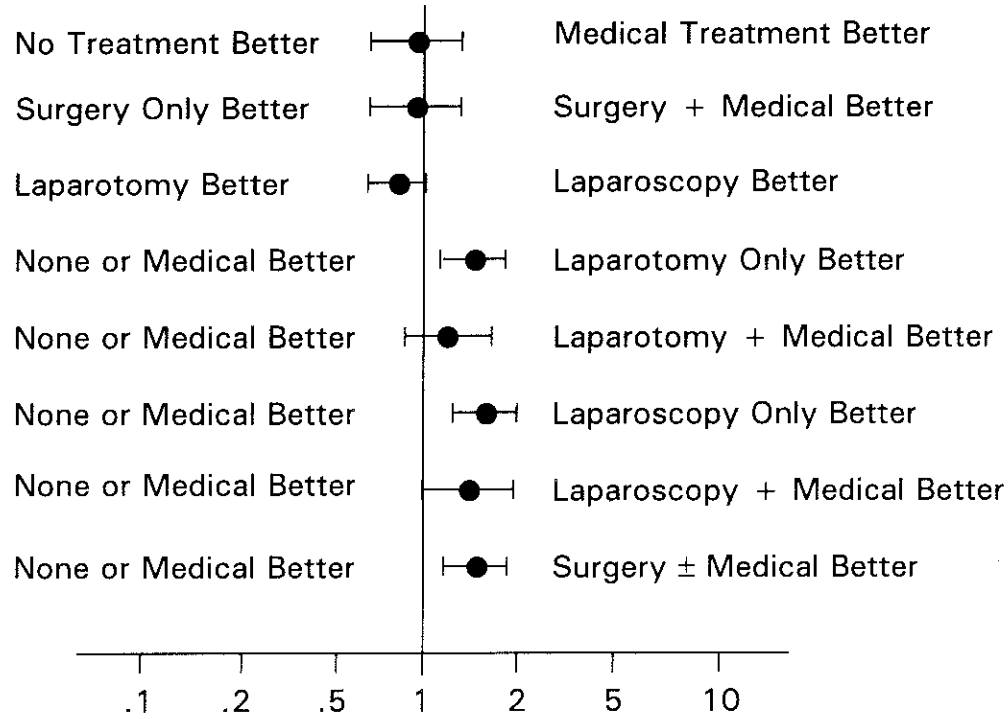

FIG 1. Summary of meta-analysis estimates of relative risk of pregnancy (point estimate and 95% confidence interval) for different endometriosis treatments. From Adamson GD, Pasta DJ: Surgical treatment of endometriosis-associated infertility: meta-analysis compared with survival analysis. *Am J Obstet Gynecol* 171(6):1488–1505, 1994 [46].

increase in fertility can be demonstrated with these medications when compared with expectant management; nor has any medication proven superior to danazol in this regard. Use of ovarian suppression also delays fertility in that the patient is unable to conceive while being medicated for several months. There is also additional cost and associated side effects, including bone loss. Thus, there appears to be little or no role for primary medical therapy in the treatment of endometriosis-associated infertility.

Ovarian suppression has been used as an adjunct to surgery in an attempt to improve subsequent pregnancy rates. The combined evidence indicates that medical treatment following surgery is not better than surgery alone, whether the surgical approach is via laparoscopy or laparotomy [46]. Therefore, medical therapy does not have a role in the treatment of endometriosis-associated infertility, either after surgery (laparoscopy or laparotomy) or alone. A summary of the meta-analysis estimates for the various comparisons is presented in Figure 1.

Presurgical ovarian suppression has also been suggested to be a beneficial adjunct. Improved pregnancy rates have been reported with presurgical medical treatment using danazol or GnRH agonists. However, these data and those suggesting improved technical results, reduced adhesions, and reduction in blood flow and inflammation are sufficiently inconclusive, so that preoperative ovarian suppression cannot yet be recommended.

Surgery. In patients with minimal or mild endometriosis, laparoscopic treatment has been used frequently, because treatment can be accomplished easily during diagnostic laparoscopy [6]. However, the ablation or removal of endometriosis implants can increase the risk for postsurgical adhesion formation. While an association clearly exists between even early-stage disease and reproductive dysfunction, it has been unclear whether or not there is a cause–effect relationship between minimal/mild disease and infertility [47]. The decision to treat minimal or mild endometriosis has been based on the nature and location of the lesions, on the potential

of the disease to become more advanced, and on the presence of pain symptoms. In light of the difficulties in evaluating the data in the literature, the lack of rigorous clinical studies showing an improvement in fertility, and the variable length of follow-up in infertility studies, the conventional wisdom has been that surgical treatment for minimal or mild endometriosis does not confer an advantage over expectant management. A meta-analysis of nonrandomized trials suggested that surgical treatment of early-stage endometriosis-associated infertility might be of value; however, there was sufficient heterogeneity among the studies to diminish confidence in such a conclusion. The average pregnancy rate from several studies evaluating the surgical approach was approximately 58%, compared with an average pregnancy rate following expectant management of approximately 45% [2,46–48] (Table I). However, the average monthly fecundity rate (when it could be calculated) for expectant management was 6.8%. This was not significantly different from the monthly fecundity rate following surgery. Thus, the effectiveness of surgery for minimal or mild endometriosis has been difficult to demonstrate.

Recently, data have been reported that support the surgical approach to infertile patients with minimal or mild endometriosis. In a prospective, multicenter, double-blinded, controlled, randomized study by Marcoux and colleagues in a Canadian collaborative trial named ENDOCAN, surgical treatment by laparoscopy resulted in a significantly higher pregnancy rate (37.5% vs. 22.5%, p = 0.002) [49]. This study provides convincing evidence that surgery is beneficial in the treatment of minimal or mild endometriosis-associated infertility. Shortly thereafter, however, a second multi-center study demonstrated a live birth rate of 19.6% in the treatment group and 22.2% in the controls within 1 year of surgery. In summary, the issue of efficacy of surgery in the enhancement of early-stage endometriosis-associated infertility remains unclear. There may well be an advantage to treatment, but its effect is most likely small. Even if ENDOCAN is correct, the number needed to treat (NNT) to produce one additional pregnancy is 7.7 surgeries.

It is widely accepted that endometriosis of sufficient severity to cause distortion of the pelvis (Stages III and IV) impairs fertility by interfering with oocyte pickup and transport. Such anatomic distortion is commonly approached via surgery for all manners of disease, and endometriosis is no exception. However, a low background pregnancy

TABLE I
Estimated cumulative life-table pregnancy rates by treatment group for different stages of endometriosis.

	Entire Patient Population					*Endometriosis-only Subset*				
		No. Pregnant	*Pregnant (%)*				*No. Pregnant*	*Pregnant (%)*		
	No.	*in 3 y*	*1 y*	*2 y*	*3 y*	*No.*	*in 3 y*	*1 y*	*2 y*	*3 y*
Minimal/Mild										
No treatment	15	10	53.3 ± 12.9*	66.7 ± 12.2	66.7 ± 12.2	13	9	61.5 ± 13.5	69.2 ± 12.8	69.2 ± 12.8
Medical treatment	44	20	26.5 ± 7.2	53.0 ± 8.9	62.3 ± 9.3	32	13	25.6 ± 8.4	47.7 ± 10.2	55.2 ± 11.2
Laparoscopy	241	122	43.6 ± 3.5	59.6 ± 3.8	67.8 ± 4.1	134	70	45.5 ± 4.7	60.4 ± 5.1	70.3 ± 5.4
Laparotomy	46	28	55.7 ± 7.9	65.6 ± 7.9	74. 3 ± 8.1	13	6	38.0 ± 15.1	50.4 ± 16.4	64.5 ± 16.8
Moderate/Severe†										
Laparoscopy	120	52	29.1 ± 4.5	50.8 ± 5.6	62.2 ± 6.2	48	25	32.2 ± 7.5	70.0 ± 9.0	82.0 ± 8.5
Laparotomy	102	37	23.8 ± 4.5	36.7 ± 5.3	44.4 ± 5.6	15	5	20.0 ± 10.3	26.7 ± 11.4	33.3 ± 12.2

*Values are estimates ± SE.
†Eleven patients treated nonsurgically have been excluded from the entire patient population.
Three patients treated nonsurgically have been excluded from the endometriosis-only subset.
From Adamson GD, Hurd SJ, Pasta DJ, Rodriguez BD: *Laparoscopic endometriosis treatment: Is it better? Fertil Steril* 59(1):35–44, Jan 1993 [48].

rate, approaching zero, in these women and numerous uncontrolled trials documenting that pregnancies do occur after reparative surgery suggests the value of this approach. As a result, few data exist regarding no treatment or medical treatment, and no prospective randomized studies with untreated controls have been reported. The available evidence supports the surgical approach compared with the nonsurgical approach for invasive, adhesive, and/or endometriotic disease.

The laparoscopic approach using excisional techniques has been described in the treatment of infiltrating cul-de-sac endometriosis, often an area of difficult dissection [31,32]. In partial or complete cul-de-sac obliteration, 34 of 46 (74%) infertile couples achieved pregnancy. Of the women who conceived, more than one laparoscopy was performed in 13 of 34 couples. Comparisons of laparoscopy versus laparotomy in the treatment of complete endometriotic posterior cul-de-sac obliteration and infertility show life-table pregnancy rates of approximately 25% at 2 years for either laparoscopy or laparotomy. Other reports support the conclusion that the results obtained by the laparoscopic treatment approach to extensive cul-de-sac and rectovaginal endometriosis are equivalent to the results obtained at laparotomy when performed by experienced laparoscopists.

Patients with endometriosis as the only infertility factor have similar crude pregnancy rates for all stages whether treated with laparoscopy or laparotomy [46,48]. Life-table analysis of patients without other infertility factors, however, revealed that laparoscopy was similar to laparotomy for minimal/mild disease and superior to laparotomy for moderate/severe disease. Survival analysis with multiple fixed covariates concurs with these findings in that laparoscopy was significantly better than laparotomy in the endometriosis-only group (87% higher pregnancy rate, $p = 0.031$). In the endometriosis-only group, survival analysis with multiple fixed covariates concurred with the findings that laparoscopy was superior. However, in a meta-analysis of studies comparing laparoscopy with laparotomy, the observed difference in pregnancy rates was not significant [46]. A possible explanation for the differences between these analyses is that meta-analysis does not account for the duration of time to pregnancy, only the final pregnancy rate. Moreover, patients treated by laparotomy generally had longer follow-up, allowing for more time to conceive. Operative laparoscopy may allow for superior results compared to laparotomy with respect to the re-formation of adhesions excised at the initial surgery. Although this has yet to be demonstrated conclusively, studies have suggested that de novo adhesion formation is less frequent following operative laparoscopy [50]. In light of the evidence supporting the equivalent if not better outcome of laparoscopy compared to laparotomy, the laparoscopic approach is preferable in most cases of endometriosis-associated infertility.

Surgery Compared With Other Treatments. Results of endometriosis treatment with surgery, and laparoscopy in particular, appear superior to all other types of treatment. This conclusion is based on numerous large studies, including life-table analysis, survival analysis with fixed covariates, meta-analysis, prospective randomized trials, and summary of all the literature. Each study has its own deficiencies, but all have shown results favoring surgery [2,25,46–49,51]. A large study of 579 patients with prospectively recorded data carried out to evaluate pregnancy rates following laparoscopy for endometriosis showed that laparoscopy pregnancy rates were equal to or higher than other treatment options for the entire population of 579 patients, as well as an endometriosis-only subset consisting of 258 patients with at least one normal tube and fimbria, and normal male factor (Table I) [48]. Laparoscopic treatment of endometriosis was found to result in equivalent or higher pregnancy rates than other treatments, whether disease was minimal, mild, moderate, or severe. These differences were up to 101% better than with other treatment modalities and could consequently be of clinical consequence to the patient. Pregnancy rates at 2 years following surgery were approximately 60% for minimal/mild disease, 50% for moderate disease, and 40% for severe/extensive disease.

Pregnancy rates following medical treatment usually are 5% to 10% lower at 2 years, and the pregnancies take longer to occur, especially with medical treatment that consumes 6 or more months of time. The pregnancy rate per month is about 4% and stays the same for about 15 months after surgery, and then decreases fairly rapidly to about 2% per month. The difference in rates between surgical and medical therapy is primarily due to lost time providing medical treatment. The time saving of up to 6 months is important to

women suffering infertility, especially older women, since their fertility may decrease during a half-year of treatment. Meta-analysis of studies comparing surgical treatment with nonsurgical treatment confirms the superiority of surgical treatment, with crude pregnancy rates estimated to be 38% higher than with nonsurgical treatment. Meta-analysis comparing laparoscopy with medical or no treatment found strong evidence favoring operative laparoscopy, with the relative risk for pregnancy being 1.47. Meta-analysis also confirms that medical treatment following surgery does not improve pregnancy rates. No data support the use of preoperative hormonal suppression.

We are developing an evidence model, which is being prepared for publication, that has also been used to clarify the clinical questions that needed to be answered. It is based on an exhaustive review of the English-language literature since 1975, which identified 1,046 potentially relevant citations of papers concerning endometriosis and infertility treatment. A review of all of these papers identified 223 that had usable pregnancy rates and could be analyzed. Preliminary analysis again confirmed that surgical treatment was superior to medical or no treatment for all stages of disease. Pregnancy rates for infertile patients with minimal or mild endometriosis in studies reporting comparison of medical or laparoscopy treatment showed laparoscopy pregnancy rates to be higher than medical pregnancy rates. It is not known what impact extensive and/or invasive peritoneal disease alone has on pregnancy rates.

TABLE II
Pregnancy rates following treatment for unexplained infertility.

Treatment	*Monthly Fecundity (%)*
No treatment	3
IUI	4
Clomiphene	6
Clomiphene plus IUI	18
Gonadotropin	8
Gonadotropin plus IUI	18
IVF	23
GIFT	26

From Guzick et al: *Fertil Steril* 70(2):207–213, 1998 [10].

Ovarian Stimulation. Controlled ovarian hyperstimulation can be performed with either clomiphene citrate (CC) and/or gonadotropins, often in conjunction with intrauterine insemination (IUI) [10,56]. These treatments are intended to increase the overall fecundity and do not cause regression of endometrial implants (Table II). Randomized trials have addressed the value of ovulation induction, and two have combined it with intrauterine insemination. These data suggest a control population fecundity of 2% to 4.5% per cycle, and for the treated population of 9.5% to 15%. From these results it is apparent that fertility can be hastened in women with endometriosis by using COH and IUI. There is a wide range of success reported, with cycle fecundity with CC-IUI increasing the baseline fecundity from 25% to 200%, and with gonadotropins increasing the baseline fecundity from 50% to 400%. The addition of intrauterine insemination appears to increase pregnancy rates only slightly with clomiphene but possibly double the success with gonadotropins. Baseline cycle fecundity may range from 0 to 2% per cycle with severe endometriosis, to 6% to 8% per cycle for minimal endometriosis in women less than 30 years of age. In patients without significant anatomic distortion, it could be expected that CC-IUI might create a fecundity rate of 6% to 8% per cycle or higher, and with gonadotropins, 12% to 20% per cycle. Randomized controlled studies of COH/IUI treatment in moderate or severe endometriosis are lacking. The expectation, however, would be for no improvement in pregnancy rates because of the high probability of significant anatomic distortion that could interfere with the mechanism of oocyte transport to the fallopian tube.

Multiple pregnancy, with approximately 25% twins, 5% triplets, and 2% quadruplets, occurs. Severe ovarian hyperstimulation syndrome occurs in approximately 1% of patients, with moderate ovarian hyperstimulation occurring in 5% to 7% of patients. About one patient in 300 requires hospitalization for ovarian hyperstimulation syndrome. Ectopic pregnancy occurs in approximately 5% of patients. The majority of pregnancies occur within two to four cycles of treatment. In very young patients with otherwise excellent prognosis, up to 6 cycles of ovarian stimulation might occasionally be indicated. Birth defect rates do not differ from the general population.

ART (Assisted Reproductive Technology). Results for 1997 from the United States IVF Registry gave a

27.9% delivery rate per retrieval for IVF. Pregnancy rates depend on patient age, ranging from about 35% per cycle at age 30 to 15% per cycle at age 40 [11]. There are no convincing data that one type of ART is superior to another. Only one randomized controlled study looked at IVF versus no treatment for 6 months in endometriosis patients, but the study had only 21 patients in the comparison groups, making conclusions impossible. Another examined the issue in a retrospective cohort study and was unable to demonstrate a significantly higher cumulative pregnancy rate between women undergoing IVF and untreated women over a 3-year follow-up period [53].

The impact of the diagnosis of endometriosis on outcomes with IVF treatment is not yet clear. There are no randomized clinical trials to answer several open issues, and cohort trials have been inconclusive. Several studies have shown patients with endometriosis have lower pregnancy rates compared with patients with tubal factor infertility. Further categorization of patients into mild and severe endometriosis groups revealed no difference in outcome in patients with mild disease, but a significantly lower pregnancy rate in patients with severe disease [53]. Some data suggest a deleterious effect on outcome because of difficulty in monitoring ovaries, reduced response to gonadotropins, reduced number of oocytes retrieved, reduced fertilization rates, reduced implantation rates, and impaired oocyte or embryo quality. Support for the poor-oocyte theory comes from the oocyte donation model, where lower pregnancy rates from oocyte donors with endometriosis and no decrease in pregnancy rates in oocyte recipients with endometriosis were observed [54–56]. Other studies, however, have not found any difference in IVF success rates between patients with and without endometriosis, and the SART data show no difference overall for endometriosis pregnancy rates compared with other diagnostic categories.

With respect to the effect of disease stage on ART outcome, there are only observational studies [19]. Conclusions have been hampered by the limitations of the classification system and the conflicting and relatively poor-quality data. With laparoscopic oocyte retrieval there may be a reduced pregnancy rate in more severe stages because of difficulty accessing the ovaries, but with transvaginal retrieval there is probably no difference. However, no studies have had the power to evaluate the impact of extensive disease with AFS score of >71, a stage of disease that appears in non-ART treatments to confer a poorer prognosis. With respect to endometriomas, there are no randomized trials, and cohort data are conflicting [57–59]. Small endometriomas may not matter and large endometriomas may. Pelvic abscess has been reported following egg retrieval in patients with endometriomas, thus providing a potential indication for pre-IVF surgical treatment in some patients.

The question of whether ovarian suppression prior to IVF is beneficial requires further study. It is clear that down-regulation with GnRH agonist in any patient produces higher pregnancy rates, but it is not known whether 2 weeks, or up to 6 months, is superior. Some data support the use of ovarian suppression for 4 to 8 weeks prior to in vitro fertilization (IVF) for women with severe endometriosis [60].

In light of the potential adverse effects of endometriosis on the oocyte, consideration of surgical treatment before initiating IVF cycles seems reasonable. Improvement in success rates, however, has not been demonstrated using surgical treatment of endometriosis before IVF. Moreover, no difference in pregnancy rates or live birth rates was observed between patients who were treated or not treated for endometriosis at the time of GIFT. Observed reduced pregnancy rates in some studies may also be attributable to reduced ovarian function because of ovarian endometriotic disease and/or prior ovarian surgery, making it mandatory to preserve ovarian volume and function during any surgical procedure. Frequently, surgery has been performed earlier during the course of the infertility work-up and treatment. It is also not clear whether the surgical treatment of endometriosis contemporaneously with GIFT is beneficial, although one randomized study showed that the GIFT pregnancy rate was not affected while following failed GIFT the spontaneous pregnancy rate was higher in the surgically treated group [61]. Another large retrospective study showed no such statistical differences [62].

While it is probably self-evident that IVF is of value in advanced disease due to the very low background pregnancy rate and the tangible rate of success with the procedure, the value of this approach in early-stage disease is as yet unproven. In other words, while pregnancies certainly occur quite rapidly with IVF in women with endometriosis or any other diagnosis, it is unclear whether one cycle

TABLE III
Pregnancy rates following treatment of endometriosis-associated infertility.

		Monthly Fecundity (%)		
Treatment	Stage:	*Minimal/ Mild*	*Moderate*	*Severe*
Expectant		3	3	0
Ovarian suppression*		3	4	1
Surgical		5	5	3
IVF (per cycle)		28	28	25
GIFT (per cycle)		30	30	20

*After discontinuation of ovarian suppression medication

of IVF is comparable to 1 month, 6 months, 2 years or longer of attempting conception naturally.

The assisted reproductive technologies of in vitro fertilization (IVF) and gamete intrafallopian transfer (GIFT) can be used effectively to treat infertile patients with endometriosis following failed treatment. They are also sometimes appropriate in older women with extensive endometriosis and/or adhesions who do not have pelvic pain or endometriomas and for whom the prognosis following surgery would be limited. It is important to consider confounding variables when deciding whether to operate on a patient. Patients who are older than 35, have duration of infertility longer than 3 years, no prior pregnancy, known extensive endometriotic lesions, adhesions, or tubal damage, or have had multiple operations have a much poorer prognosis.

Overall, while IVF is clearly worthwhile, its degree of value, cost effectiveness, and optimal method of employment has not yet been satisfactorily determined.

ALGORITHM FOR MANAGEMENT OF ENDOMETRIOSIS

Endometriosis is obviously an extremely complex medical condition, and treatment is similarly complicated [63]. Treatment needs to be based on each patient's individual circumstances and objectives (Table III). However, the algorithm shown in Figure 2 is suggested as a possible model that can be modified for individual patients. Patients with pelvic pain and suspected endometriosis can be initially managed with NSAIDs and continuous oral contraceptives for 3 months followed by 1 week's withdrawal, with continued repetition of this regimen. For patients with suspected endometriosis and infertility, if all other infertility factors are appropriately evaluated and found to be acceptable, it is reasonable in those under age 37 to attempt 3 to 4 cycles of clomiphene citrate 100 mg/day for cycle days 3 through 7. Intrauterine insemination probably increases pregnancy rates slightly when used in conjunction with clomiphene. Appropriate patients under age 32 may receive up to 6 cycles.

If the pain patient fails to have relief, or the infertility patient fails to conceive on the above regimens, laparoscopy is indicated to confirm the suspected diagnosis of endometriosis. Whether the patient's symptoms are pain or infertility, surgical treatment involving complete laparoscopic resection of the disease should be performed at the time of diagnosis if the surgeon is capable of so doing. The only exception to this approach is the young woman with infertility as her only symptom and extensive superficial peritoneal and/or ovarian disease. Treatment of such lesions may increase pregnancy rates but also may result in pelvic adhesions. Pain patients should generally receive continuous oral contraceptives postoperatively, as described above. For infertility patients, controlled ovarian hyperstimulation and intrauterine insemination postoperatively for 3 to 6 months with clomiphene and/or 3 to 6 months with gonadotropins will increase pregnancy rates.

IVF is usually considered after expectant management and/or ovarian hyperstimulation with intrauterine inseminations has failed following surgery.

If the patient has adequate surgical extirpation of the disease, no further postoperative ovarian suppression is indicated, except for oral contraceptives for pain patients. If pain recurs, GnRH agonists should usually be the first line of treatment. For infertile patients who fail to conceive, a second-look laparoscopy at 6–18 months may sometimes be indicated, possibly with GIFT performed at the same time. If extensive endometriosis, adhesions, or tubal abnormalities are found, IVF should be considered within 0 to 12 months following surgery.

If the pain patient does not have operative laparoscopy at the time of diagnosis, or has incom-

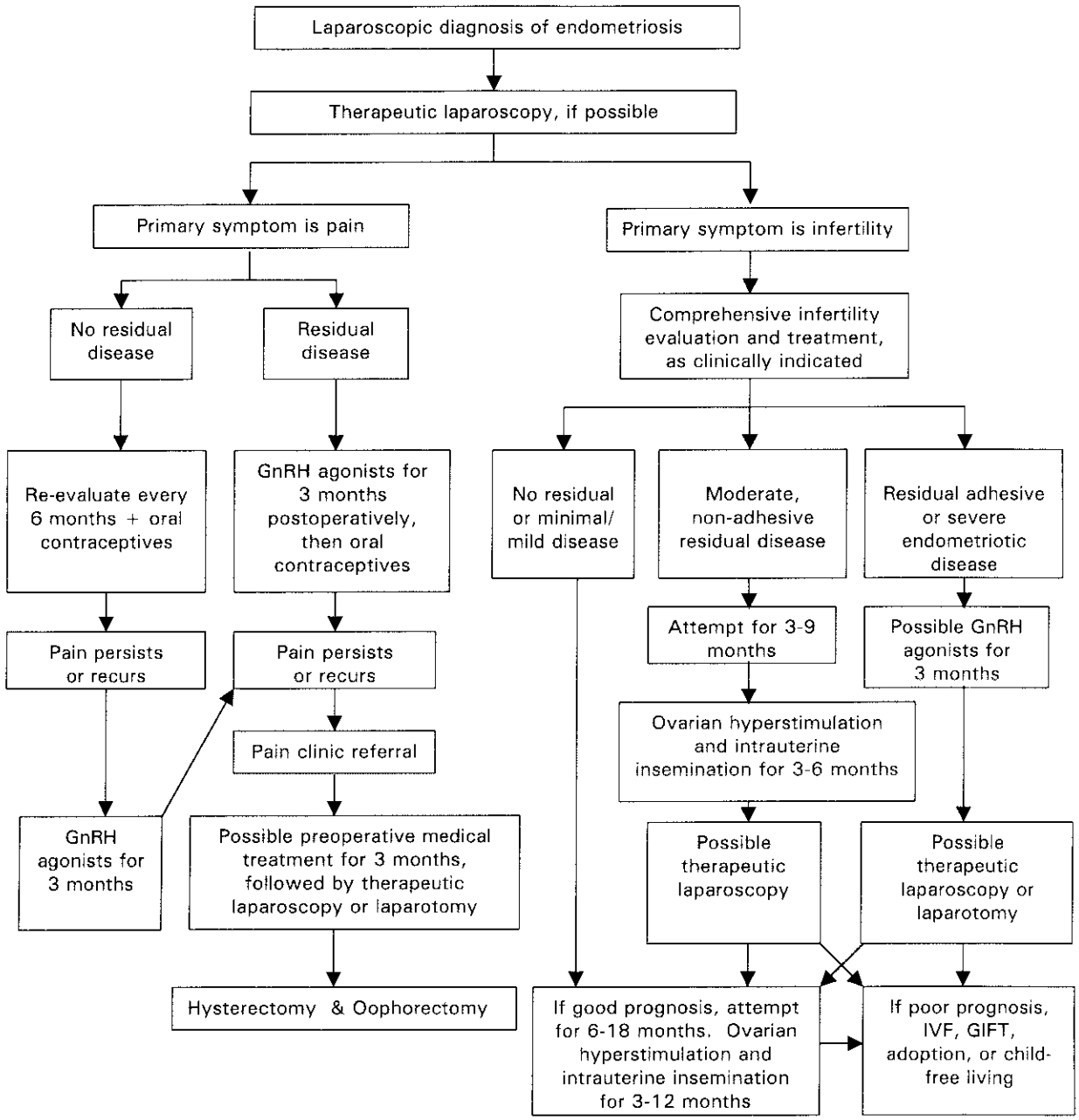

FIG. 2. Postlaparoscopy management of endometriosis. Modified from Adamson GD: Laparoscopic treatment of endometriosis, in Adamson GD, Martin DC (eds): *Endoscopic Management of Gynecologic Disease.* Philadelphia, Lippincott-Raven, pp 147–187, 1996 [6].

plete resection of endometriosis, there is the option of a repeat laparoscopy or laparotomy, most likely by a more experienced surgeon specializing in endometriosis, or use of GnRH agonists or danazol for 3 to 6 months. GnRH agonists are generally preferred because of their more favorable side effect profile. Overall, the available data do not support the routine perioperative use of GnRH agonists or ovarian suppression therapy, but these may be of value in selected patients. Failure to manage pain success-

fully with surgical and/or ovarian suppression should result in referral to pain specialists for a comprehensive approach to the pain. Such an option should be discussed with the patient at her first consultation and integrated into the treatment plan.

For infertility patients who have not had operative resection, or have inadequate resection, minimal or mild disease (no adhesions, no invasive lesions, no endometriomas) needs no further treatment. Patients with moderate or advanced disease should be referred for laparoscopy or, occasionally, laparotomy. Ovarian suppression should not be used.

Infertile patients who do not conceive within 6 to 15 months should have a repeat laparoscopy for treatment and/or assisted reproductive technologies such as IVF and/or GIFT (Figure 2), depending on the patient's age and other infertility factors. Ovarian suppression with GnRH agonists for 2 to 6 weeks before ovarian stimulation with gonadotropins increases success rates. IVF is indicated in almost all patients who have failed surgical treatment and/or ovarian hyperstimulation treatment, and occasionally as a first treatment instead of surgery in patients with extensive disease and/or other infertility factors.

THE FUTURE

We have much to learn about endometriosis. More detailed evidence-based meta-analysis and prospective randomized studies are being performed to help improve our clinical guidelines. Development of a scoring system that correlates with severity of reproductive dysfunction will be a significant contribution to endometriosis-associated infertility research [19]. Accounting for differences among control and treatment groups by using appropriate statistical methods is required given the dearth of prospective randomized trials. As more studies are conducted utilizing sophisticated designs and statistical methods, more definitive conclusions should be possible regarding the optimal treatment approaches for endometriosis-associated infertility.

The future holds promise for better management of endometriosis. GnRH antagonists are now becoming available, and may eventually allow for intermittent treatment of endometriosis. Add-back therapy will be further refined, probably allowing longer treatment protocols. Surgical capabilities will continue to increase, although fewer surgeons will be performing difficult endometriosis operations. IVF results will continue to improve and will be used for many more endometriosis patients.

Basic research currently underway should give us a better understanding of β3 integrins, aromatase inhibitors, immunology and the potential role of immunotherapy in new therapeutic approaches [64]. An international study to determine the genetic basis of endometriosis is currently underway, and may lead to much more successful treatment in the years ahead [65]. Treatment at the beginning of life will become a reality in this century through the use of preimplantation genetic diagnosis. All these advances should allow us eventually to diminish markedly the personal and social impact of endometriosis.

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