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Original Article

Combined Surgical and Hormone Therapy for Endometriosis is the Most Effective Treatment: Prospective, Randomized, Controlled Trial

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ABSTRACT **Study Objective:** To evaluate 3 therapy strategies: hormone therapy, surgery, and combined treatment.
Design: Prospective, randomized, controlled study (Canadian Task Force classification I).
Setting: University-based teaching hospital.
Patients: Four hundred fifty patients with genital endometriosis, aged 18 to 44 years, before first laparoscopy.
Interventions: Patients were randomly assigned to 1 of 3 treatment groups: hormone therapy, surgery, or combined treatment. Patients were reevaluated at second-look laparoscopy, at 2 to 2 months after 3-month hormone therapy in groups 1 and 3 and at 5 to 6 months in group 2 (surgical treatment alone). Outcome data were focussed on the endometriosis stage, recurrence of symptoms, and pregnancy rate.
Measurements and Main Results: All treatment options, independent of the initial Endoscopic Endometriosis Classification stage, achieved an overall cure rate of $\geq$50%. A cure rate of 60% was achieved with the combined treatment, 55% with exclusively hormone therapy, and 50% with exclusively surgical treatment. Recurrence of symptoms was lowest in patients who received combined treatment. Significant benefit was achieved for dysmenorrhea and dyspareunia. An overall pregnancy rate of 55% to 65% was achieved, with no significant difference between the therapeutic options.
Conclusion: In the quest to find the most effective treatment of genital endometriosis, this clinical randomized study shows the lowest incidence of recurrence with combined surgical and medical treatment and improved pregnancy rate in any medically treated patients with or without surgery. The highest cure rate (Endoscopic Endometriosis Classification stage 0) for endometriosis was also achieved in the combined treatment group. Journal of Minimally Invasive Gynecology (2013) 20, 473–481 © 2013 AAGL. All rights reserved.

Keywords: Combined treatment; Endometriosis; Hormone therapy; Infertility; Laparoscopy; Prospective studies; Recurrence; Reoperation

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Endometriosis is considered the second most common benign female genital disease after uterine myoma. It has been defined as the presence of endometrial glands and stroma outside of the internal epithelial lining of the cavum uteri. Symptoms include chronic pelvic pain, dysmenorrhea, deep dyspareunia, cyclical bowel or bladder symptoms (e.g., dyschezia, bloating, constipation, rectal bleeding, diarrhea,

and hematuria), subfertility, abnormal menstrual bleeding, chronic fatigue, and low back pain [1].

Approximately 50% of teenagers and as many as 32% of women of reproductive age operated on because of chronic pelvic pain or dysmenorrhea have endometriosis. The percentage of women treated for infertility with confirmed endometriosis is 9% to 50%. The prevalence of endometriosis in the general population remains unclear because symptoms are diverse and nonspecific [2,3].

The interval between the first unspecific symptoms and the medical diagnosis of endometriosis is about 7 years. The condition is usually diagnosed for the first time in patients between the ages of 20 and 40 years. In cases of secondary sterility, the frequency increases parallel to the time since the last pregnancy: $<$5 years, 7%; 5 to 10 years, 19%; and $>$10 years, 26% [4].

Because the pathogenesis of endometriosis is not clearly understood, causal treatment is not possible. Treatment options include expectant management, analgesia, hormone therapy, surgical intervention, and combined medical treatment before and/or after surgery. Inasmuch as endometriosis growth is promoted by estrogen, various medical therapies can be administered [5,6].

Treatment Options

Medical Treatment

In the past, the primary treatment strategy was administration of gestagens, and later danazol and gonadotropin-releasing hormone (GnRH) analogues [5]. It is now supplemented by an add-back therapy and progesterone (e.g., Visanne). To prevent adverse effects of GnRH agonists such as bone demineralization, vasomotor symptoms, and mood swings, a serum estradiol concentration of $\sim$60 pg/mL is required [5,7,8].

Targeted Treatment

Research has focussed on inhibiting the interaction of various mediators that maintain the illness via inflammatory processes, vascularization, and cell proliferation. Specific aromatase inhibitors (e.g., letrozole, anastrozole, and exemestan) or selective cyclooxygenase-2 inhibitors (e.g., celecoxib and rofecoxib) are of great interest and have been studied in clinical trials [9].

Surgical Treatment

Endometriosis is a progressive disease that can cause anatomical destruction of the reproductive organs; thus, surgical therapy has an important role. In advanced stages, pain and sterility are predominantly caused by organ damage, fibrosis, and adhesions, thus constituting a clear indication for surgical intervention. Early laparoscopy can prevent any delay in diagnosis of the disease or in symptom progression [10]. Risk factors and disadvantages of laparoscopy include damage to organs adjacent to the affected areas and postoperative complications such as adhesion formation or infection [11,12]. Symptom relief is achieved in most patients after successful ablation/resection of endometriosis and adhesiolysis. Nevertheless, the recurrence rate is as high as 40% at 10-year follow-up [13–15].

Combined Treatment

The first structured therapeutic pathway was introduced by Mettler and Semm [16]. It involves diagnostic laparoscopy, removing all visible endometriosis foci as far as possible, a three to six-month endocrine therapy and a subsequent second-look laparoscopy with resection of residual foci, adhesiolysis and reconstruction of organs [16–18].

Despite maximal efforts, the therapy of first choice in the management of endometriosis is still unclear [1,4]. In the present 3-year study, 450 patients with endometriosis underwent 1 of 3 therapeutic strategies (medication, surgery, or combined treatment) at our Department of Obstetrics and Gynecology (Kiel University, Kiel, Germany). The objective was to determine the most successful available endometriosis therapy.

Material and Methods

Patients

Patients were selected from those treated at our department. All patients were allocated exactly according to the random principle. Informed consent forms were completed by all patients. The present study, which included surgery, medical therapy, and a selected second-look operation, was approved by the Ethical Committee of the Christian-Albrechts-University (Kiel, Germany) (D 42602). Each patient signed an informed consent form for use of specimens and clinical data.

The study comprised 450 patients, aged 18 to 44 years, with symptomatic endometriosis in whom 2 consecutive laparoscopic interventions were to be assessed. All patients treated at our department who had no exclusion criteria and agreed to the trial profile were recruited for the study. Each of the 3 groups consisted of 150 patients, 40 of whom did not return for second-look pelviscopy. Symptoms in the 450 patients with pain and/or infertility were analyzed within the framework of pelviscopic treatment. Four hundred ten patients from the original cohort returned for second-look laparoscopy (Fig. 1).

Exclusion Criteria

Previous surgery or hormone therapy for endometriosis were exclusion criterion, as were deep infiltrating endometriosis with bladder or rectum excision. The treatment of deep infiltrating endometriosis with big lesions affecting bowel and/or urinary tract, favorably diagnosed before surgery, was performed via extensive laparoscopic resection.