Contr. Gynec. Obstet., vol. 16, pp. 150-155 (Karger, Basel 1987)

High-Dose Medroxyprogesterone Acetate and Danazol in the Treatment of Endometriosis

Sakari Telimaa, Jukka Puolakka, Lars Rönnerberg, Antti Kauppila
University of Oulu, Oulu, Finland

Studies on cytosol endometrial estrogen and progestin receptor concentrations and 17 β -hydroxysteroid dehydrogenase activity have shown that the effects of danazol and medroxyprogesterone acetate (MPA) are similar. Therefore we conducted a placebo-controlled study to compare danazol (600 mg/day) and MPA (100 mg/day) in the hormonal treatment of mild-moderate endometriosis. The duration of treatment was 6 months. Laparoscopy was performed before the trial and 6 months after the treatment. Sixteen patients receiving MPA, 18 patients receiving danazol and 17 receiving placebo completed the study.

The resolution of the peritoneal endometriosis implants was similar in the MPA (63%) and danazol (60%) groups, results differing significantly from the placebo effect (18%). MPA and danazol significantly alleviated endometriosis-associated pelvic pain, lower back pain and defecation pain and they did not differ from each other. In comparison with placebo, MPA appeared to be less androgenic than danazol, while anabolic side effects were similar.

High-dose MPA is thus a useful alternative in the hormonal treatment of endometriosis.

The Impact of Gestrinone upon the Natural History of Endometriosis

E.J. Thomas, I.D. Cooke
University Department of Obstetrics and Gynaecology,
The Jessop Hospital for Women, Sheffield, England

There is no placebo-controlled trial of any treatment of endometriosis and therefore there is no description of the natural history of the disease or complete validation of the efficacy of drug therapy. There is, therefore, debate about the need for treatment especially in asymptomatic mild and moderate disease.

Forty patients with asymptomatic endometriosis were recruited to a randomised, double-blind controlled trial of gestrinone (Roussel-UCLAF) 2.5 mg orally twice weekly. The endometriosis was diagnosed at laparoscopy and scored using the American Fertility Society System (1979). The range of scores was 1-6 (median = 2). After 24 weeks a repeat

laparoscopy was performed. Cure was defined as no visible endometriosis, improvement as a decrease in and deterioration as an increase in the score.

There were 18 evaluable patients randomised to gestrinone and 17 to placebo. In the placebo group cure was seen in 4, improvement in 5 and deterioration in 8 patients. In the treatment group cure was seen in 11 and improvement in 15 patients. No patient showed deterioration. The difference in rates of improvement ($p < 0.001$) of the disease in the treatment group and of deterioration ($p < 0.001$) in the placebo group was statistically significant.

This study has shown a natural history of deterioration of the disease in nearly 50% of patients with asymptomatic endometriosis which does not occur on treatment. This cannot be predicted for any individual and therefore it is recommended that medical therapy is prescribed in all. Gestrinone is an effective treatment of endometriosis.

Metabolic Effects of Hormonal Treatment for Endometriosis: Danazol versus LHRH-Agonist (Buserelin) Therapy

U. CirkeP, K.-W. Schweppeb, H. Ochsa, H.P.G. Schneidera
“Universitäts-Frauenklinik, Münster; bKreiskrankenhaus Ammerland,
Frauenklinik, Westerstede, FRG

Between 1979 and 1986 102 patients were treated for endometriosis. Diagnosis was made by laparoscopy or laparotomy and histological examination of suspect specimens. After confirmation of the diagnosis ‘endometriosis’, we started a 6-month treatment course with either 600 mg/day danazol (62 patients) or 900 pg/day buserelin intranasally (40 patients). Before and under therapy we checked the complete blood count, clotting parameters, electrolytes and renal function as well as liver enzymes and lipid metabolism. After treatment, the success of therapy was assessed by control laparoscopy. Complete blood count, serum electrolytes as well as renal function were unaffected by treatment of both drugs. In contrast, danazol led to a disturbance in liver function. After 6 months of therapy glutamic pyruvic transaminase (GPT) significantly rose up to 18.4 ± 5.6 U/l. Some patients presented with an even more pronounced increase of GPT as well as glutamic oxaloacetic transaminase levels, so that cessation of therapy had to be discussed. While total cholesterol, low-density lipoprotein-cholesterol and triglycerides stayed within the normal range, high-density lipoprotein (HDL)-cholesterol levels decreased significantly to 26 ± 11.3 mg/100 ml after 2 months of danazol, resulting in an increased atherogenic index. In contrast to this, buserelin caused increasing HDL-cholesterol levels. There was no effect of buserelin on clotting parameters. Danazol lowered fibrinogen concentrations to 164 mg/100 ml after 3 months and 151 mg/100 ml after 6 months, respectively. This effect was outweighed by increased plasminogen concentrations

(15.9 mg/100 ml after 6 months of danazol). Consequently there were no bleeding complications during control laparoscopy.

We conclude that liver and lipid metabolism should be observed carefully during danazol treatment. In case of severe disturbance of these parameters an alternative in

Free Communications 152

hormonal treatment of endometriosis may be the recently introduced luteinizing hormone-releasing hormone agonist goserelin. Both drugs are known to be effective in reducing endometriotic implants.

A Comparison of the Changes in the Plasma Lipids and Lipoproteins during Therapy with Danazol and Gestrinone for Endometriosis

M.W. Bookera, P.R. Turner^b, B. Lewis^b, M.I. Whitehead^a

^aAcademic Department of Obstetrics and Gynaecology,
King's College School of Medicine and Dentistry, Denmark Hill, London;

^bDepartment of Chemical Pathology and Metabolic Diseases,
St Thomas' Hospital Medical School, London, England

Danazol and gestrinone are effective drugs for treating endometriosis. Danazol has an adverse, but reversible effect on the plasma lipids and lipoproteins. The effect of gestrinone has not previously been studied.

Twenty endometriosis patients were randomly allocated to 6 months therapy with either danazol 200 mg/day or gestrinone 2.5 mg twice weekly. Fasting blood samples were taken before, during and after treatment for a full lipid analysis by ultracentrifugation.

There were no significant changes in total cholesterol, total triglycerides, very low-density lipoprotein (VLDL) cholesterol, VLDL triglycerides, or LDL cholesterol. Both drugs produced a significant fall in the levels of high-density lipoprotein (HDL) cholesterol, HDL₂ cholesterol and HDL₃ cholesterol. There were significant differences between the two treatments and the levels returned to normal on stopping treatment.

Although a temporary lowering of the level of HDL cholesterol is an adverse effect, it is probably acceptable in view of the clinical benefits of treatment.

Endocrine and Morphological Changes during GnRH Analogue Treatment (Suprefact) for Endometriosis

C. Melega^a, M. Filicoria, A. Pareschi^a, G. Possati C. Flamigni¹, S. Barnabei^b

^aDepartment of Gynecologic Endocrinology of Bologna University

(Prof. C. Flamigni); ^bInd Obstetric and Gynecological Clinic (Prof. C. Orlandi),
Bologna, Italy

A potent agonist of gonadotropin-releasing hormone (GnRH; Suprefact-Hoechst) was administered to 5 patients affected by endometriosis diagnosed by laparoscopy. Classification of endometriosis was made, according to the American Fertility Society, at the time of laparoscopy. Suprefact-Hoechst was administered subcutaneously (0.3 mg twice a day) for 6 months.

Free Communications 153

During treatment, a GnRH test was performed to study hormonal responses. Ovarian and uterine dimensions were determined monthly with ultrasound scanning. Resolution of endometriosis was evaluated at the end of therapy by a second-look laparoscopy.

First Experiences in Treatment of Endometriosis with the GnRH Analogue Buserelin

T. Schumacher, K. Böhler, E.M. Schindler, M. Zwirner, A.E. Schindler
University of Essen, Department of Obstetrics and Gynecology, Essen, FRG

Buserelin is a long-acting gonadotropin-releasing hormone (GnRH) analogue. It can be administered intranasally by a nasal spray dispenser. Continuous treatment results in a down-regulation of the GnRH receptor sites of the pituitary. Therefore, the serum estrogen levels are diminished by inhibition of the ovaries. The aim of the presented study was to prove the possible use of buserelin in treatment of endometriosis.

Patients and Methods

The study includes 20 patients with endometriosis. The endometriosis was classified before treatment according to the endoscopic endometriosis classification (EEC) published by Semm. There were 8 patients with EEC level I, 8 with EEC level II, 3 with EEC level III and 1 with EEC level IV. The treatment with 900 µg buserelin intranasally was started on the first day of the next bleedings and continued for 6 months. During treatment, monthly clinical examinations were performed. After treatment, a new classification of the endometriosis according to the EEC was performed.

Results

The percentage of patients with irregular bleedings dropped from 60% after one month of therapy to 10 % after 6 months. After one month, 20 % suffered from hot flushes, after 6 months however 55%. There was no significant weight gain or weight loss during the therapy.

The serum luteinizing hormone and follicle-stimulating hormone levels were all within the normal range and showed no significant change during therapy. The serum

estradiol (E2) levels dropped from 195 pg/ml significantly to 46.6 pg/ml after a 6-month therapy. However, until the fourth month there were unsupposed E2 spikes to be seen. All serum progesterone levels were below 2.6 ng/ml during treatment. All testosterone levels were in the normal range and showed no changes during treatment.

After treatment, there was no more endometriosis to be seen in 16 out of 20 patients. There were 2 patients with EEC level I, 1 with EEC level II and 1 with EEC level III. In summary, buserelin was very effective in the treatment of endometriosis. Because our study has just finished, the total pregnancy rate after therapy of endometriosis with buserelin is still unknown. However, 2 patients with sterility for several years got pregnant 2 and 3 months respectively after the end of treatment.

Free Communications 154

Long-Term Treatment of Endometriosis with LHRH Agonists Using Slow Release Systems

F. Geithövel, F. Peters, H.-P. Zahradnik, M. Breckwoldt

Department of Clinical Endocrinology, University of Freiburg, Freiburg i.Br., FRG

Six patients suffering from endometriosis (Acosta stages I to III) were treated by luteinizing hormone-releasing hormone agonists (LHRH-A). In 3 of the 6 patients buserelin (Hoechst AG, FRG) was subcutaneously infused using an osmotic minipump system (2 ML1, Alza Corp., USA) over a 12-week period. In the residual 3 patients decapeptyl (Ferring AG, FRG) encapsulated in biodegradable microcapsules was intramuscularly injected every 4 weeks over a 22- to 35-week period. 17β -Estradiol plasma levels declined into castration range within 8-17 days. The data obtained indicate the clinical utility of LHRH-A slow release systems.

Role of Laparoscopic Laser Vaporization in the Treatment of Pelvic Endometriosis and Infertility

Pierre Asmar, John D. Paulson

Reproductive Endocrinology Gynecology, Alexandria, Va., USA

Between 1979 and 1983, 293 consecutive patients with a diagnosis of infertility and mild or moderate endometriosis as the only contributing factor underwent different therapeutic modalities: expectant management, medical therapy, laparoscopic cauterization, and conservative surgery. Pregnancy rates were respectively 57% (16/28), 54% (51/95), 25% (1/4) and 84% (97/116).

Between 1983 and 1985, 296 consecutive infertility patients with a diagnosis of mild or moderate endometriosis as the only cause of their infertility were treated by laparoscopic CO₂ laser vaporization. Their overall pregnancy rate was 77% (227/296). It

included 81% (147/181) for mild and 70% (80/115) for moderate endometriosis. Pregnancy rates following laparoscopic laser vaporization were found higher than following medical or expectant therapy or laparoscopic cauterization but were comparable to conservative surgery. These results suggest that laparoscopic laser vaporization of endometriosis is an effective new therapeutic modality for infertility and endometriosis.

Endoscopic Treatment of Adenomyosis by Y AG Laser

J. Dequesne

Le Locle, Switzerland

We have made an operational hysteroscopy on patients suffering of uterine bleedings resisting conventional treatment. In 44% of the cases, we found single or associate adenomyosis and we treated them at the same time ambulatorily under paracervical

Free Communications 155

anesthesia by means of the Nd YAG laser. Therefore we have coagulated the perifocal vessels in the lesion with a power between 20 and 30W as well as the crypts for the adenomyosis up to a depth of 5-6 mm.

Four cycles after the treatment, the results show a normalization of the menogram in 80% of the cases and we have been surprised to find accessory on 18 patients having dysmenorrhea, a total remission in 67% of the cases and a partial remission in the other cases. In these 18 patients, 2 patients suffering from adenomyosis had positive pregnancy tests, but one has had a spontaneous abortion. A longer follow-up treatment is however necessary to estimate its lasting efficiency on the menogram, dysmenorrhea and pregnancy.