Low-dose danazol after combined surgical and medical therapy reduces the incidence of pelvic pain in women with moderate and severe endometriosis

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The most effective therapy for endometriosis is a matter for debate. The aim of the present randomized study was to evaluate the efficacy of low doses of danazol on recurrence of pelvic pain in patients with moderate or severe endometriosis, who had undergone laparoscopic surgery and 6 months of gonadotrophin-releasing hormone analogue (GnRHa) therapy. After surgery, 28 patients with moderate or severe endometriosis underwent therapy for 6 months with GnRHa i.m. every 4 weeks. They were then randomized into two groups: group A (14 subjects) was treated with 100 mg/day danazol for 6 months; group B (14 subjects, control) did not receive any type of therapy. After 12 months of treatment, group A had a significantly \( P < 0.01 \) lower pain score than group B. There was no significant difference between the groups in oestrogen concentrations, bone mineral density or side-effects. The results suggest that low-dose danazol therapy reduces recurrence of pelvic pain in patients with moderate or severe endometriosis, treated surgically, and has few or no metabolic side-effects.

Key words: danazol/endometriosis/GnRHa/laparoscopy/pelvic pain

Introduction

Endometriosis is a frequent pathology among women of childbearing age, with an incidence ranging from 7 to 50% (Shaw, 1988). It may be asymptomatic or associated with pelvic pain and infertility (Cook and Rock, 1991).

The therapy for endometriosis is a matter for debate. Medical therapy, alone or combined with ultrasonically guided aspiration of endometriomas, is only partially successful (Vercellini et al., 1992; Donnez et al., 1994), whereas the most effective type of surgical intervention seems to be laparoscopic. Ovarian endometriosis can often be resolved with laparoscopy, by total stripping and bipolar clotting or laser vaporization of the cyst wall (Martin, 1991; Operative Laparoscopic Study Group, 1991). Visible areas of peritoneal endometriosis can also be treated by bipolar clotting or laser vaporization. Surgical division of adhesions and interruption of neural pathways can be used to alleviate painful symptoms. Medical therapy associated with surgery may help to eradicate deep endometriotic implants, but can be used only for limited periods because of harmful side-effects. Gonadotrophin-releasing hormone analogues (GnRHa) cause hypo-oestrogenism with loss of bone mineral density and menopause-like vasomotor symptoms (Barbieri, 1990). High doses of danazol for long periods have strong androgenizing effects, including weight gain, acne, hirsutism, oily skin and hair (Neves-e-Castro and Correia, 1987) and also interfere with liver lipid metabolism, leading to a lowering of high density lipid (HDL) cholesterol concentrations. Medical therapy alone in short cycles is only partially successful because of the known capacity of deep implants to survive unfavourable hormonal conditions of brief duration (Redwine, 1992; Vercellini et al., 1994).

In a previous study, we reported that low doses of danazol, even for prolonged periods, do not create significant metabolic imbalances but have only minor side-effects, for example bloating (De Leo et al., 1997). Although at low doses (100 mg/day), danazol does not bind to oestrogen receptors, it binds stably to androgen and progesterone receptors, reducing the effects of oestrogens, impeding the proliferation of deep endometriotic implants and reducing pain. The aim of the present randomized study was to evaluate the ability of low doses of danazol to limit the recurrence of pelvic pain in patients with moderate or severe endometriosis who had undergone laparoscopic surgery and 6 months of GnRHa therapy.

Materials and methods

After laparoscopic and histological examination, 28 patients with moderate [AFS stage III (American Fertility Society, 1996), 42.8%] or severe (stage IV, 57.2%) endometriosis were recruited. Their mean age was 30.6 years ± 9.4 (SD); range 19–47 years. Patients who had previously undergone medical or surgical therapy for endometriosis were excluded, as well as those with endometriosis at AFS stages I and II. None of the patients had any other significant pathology.

All patients underwent gynaecological examination, routine analyses of blood chemistry (including lipid profile and clotting factors) and ultrasonographic examination (with a 3.5 MHz transabdominal sectorial probe and a 5.0–7.5 MHz transvaginal probe, Siemens Sonoline SL 2, Milan, Italy) before surgery.

The operation was performed under general anaesthetic by the same surgeon. The laparoscopic procedure included lysis of adhesions, bipolar clotting or excision of visible implants, emptying of cysts, capsule stripping and clotting of ovarian parenchyma of endometriomas. No endometriotic material remained following surgery.

Informed consent was obtained from each patient before starting medical therapy. After surgery, all patients underwent therapy for 6 months with GnRHa (3.75 mg triptorelin, Decapeptyl 3.75; Ipsen, Milan, Italy) i.m. every 4 weeks. They were then randomized into two groups: group A (14 subjects) received 100 mg/day danazol for
6 months and contraception (condom) was used during this period; group B (14 subjects, control) did not receive any type of therapy.

Follow-up examination took place 6, 12 and 24 months after surgery and included gynaecological examination, pelvic ultrasonography, evaluation of bone mineral density (BMD) and pain score. A 10 cm analogue scale and a verbal rating scale were used to evaluate pelvic pain and possible dysmenorrhoea. Oestriadiol was measured during the follicular phase before and 6, 9, 12, 15, 18, 21 and 24 months after surgery.

Hormone assays

Serum oestriadiol concentrations were assayed by double-antibody radioimmunoassay using commercial kits from Sorin (Saluggia, VC, Italy). Samples were assayed in duplicate at two dilutions, and those from a given subject were analysed in the same batch to avoid interassay variation. Quality control pools containing low, normal and high oestradiol concentrations were analysed in each batch of assays. The detection limit of the assay was 18 pmol/l for oestradiol. Intra- and interassay coefficients of variation were 4.2 and 4.9%.

Calculation of bone mineral density

Bone mineral density was measured by dual X-ray absorption (OSTESCAN NIM; Verona, Italy) in the distal radius of the non-dominant forearm.

Statistical analysis

Comparisons between treatments were performed by analysis of variance (ANOVA) at each time point (at the end of GnRHa treatment and after 12 and 24 months of follow-up). Comparisons within treatment groups were made by Student’s t-test for paired and unpaired data. The results were expressed as mean ± standard deviation (SD), and P < 0.05 was considered significant.

Results

Groups A and B were not significantly different with regard to age, parity or stage of endometriosis.

The patients were amenorrhoeic after the second injection of GnRH. Menstrual cyclicity returned 62 ± 8 days after the last injection of GnRH, and did not differ significantly between in the two groups. Only two women remained amenorrhoeic for 2 months after the start of danazol therapy.

BMD before therapy was within the normal range. After GnRH treatment there was a mean decrease in BMD of 2.8% (group A + group B). A partial recovery of BMD was observed at 12 months (group A 1.5%, group B 1.2%) and was not significantly different between groups. At 24 months, BMD returned to initial values in both groups (Figure 1).

Mean serum concentrations of oestradiol were 249 ± 39 pmol/l in group A and 238 ± 33 pmol/l in group B before starting the GnRH therapy and 36.7 ± 15 pmol/l in group A and 36.7 ± 11 pmol/l in group B after GnRH treatment (6 months). At 9 months, oestradiol concentrations returned to normal [160 ± 33 pmol/l in group A and 220 ± 45 pmol/l in group B (P < 0.05)]. At 12 months, oestradiol concentrations were slightly lower in group A (190 ± 51 pmol/l) than in group B (264 ± 33 pmol/l, P < 0.05). At 24 months, oestradiol concentrations returned to values which were in the normal range for both groups (group A 238 ± 44 pmol/l, group B 249 ± 55 pmol/l) (Figure 2).

Pelvic pain and dysmenorrhoea scores before surgery were not significantly different between the two groups. After GnRHa therapy (6 months), all patients had lower pain scores. At 12 months there was a significant difference in pain score in favour of group A (P < 0.01). At 24 months, pain score was significantly lower in group A, with a recurrence rate of 44% compared to 67% in group B (P < 0.05) (Figure 3).

Ultrasound examination performed 12 months after the end of danazol therapy (24 months) showed echodense areas 1.5–2.0 cm in size in the ovaries of three women in group B. However, it was not possible to determine the degree of improvement by ultrasound.

Side-effects were minor and well tolerated. There was spotting (12% of group A versus 7% of group B), bloating (16 versus 9%), headache (21 versus 13%) and weight gain (22 versus 14%).

Discussion

Endometriosis is a complex pathology for which no completely satisfactory therapy has yet been found. Surgery does not completely resolve the disease. Medical treatment with danazol and GnRHs is efficacious but not totally successful. Currently
Danazol after surgery and GnRHa reduces pelvic pain in endometriosis

The mechanism of action of danazol in the relief of endometriosis is related to its anti-progesterone and anti-oestrogen effects. Oestrogen receptor expression has been reported to be higher in eutopic than in ectopic endometrium throughout the menstrual cycle, whereas progesterone receptor expression tended to be the reverse (Jones et al., 1995).

Twelve months after the completion of danazol therapy, a significant reduction in pelvic pain persisted. No patient found the side-effects intolerable and all completed the course of therapy. Although all patients experienced an improvement in pelvic pain, we failed to observe a visible regression of endometriosis.

The results of the present study show that low-dose danazol therapy reduces recurrence of pelvic pain in patients with moderate or severe endometriosis who have undergone surgical treatment and appears to be accompanied by few or no metabolic side-effects.

The treatment of endometriosis requires individual evaluation, because the disease is often clinically complex, with the presence of different stages which require combined surgical and medical treatment.

Our results suggest that administration of danazol after 6 months of GnRH therapy does not significantly alter plasma concentrations of oestradiol and does not lead to further bone loss, while it significantly reduces pelvic pain in the long term in patients with moderate and severe symptomatic endometriosis. Further studies in a larger population are needed to confirm these results.

References


available drugs are able to induce clinical remission but do not eliminate endometriotic implants. Recurrence is therefore attributable to the persistence of such implants. Ovarian steroids induce endometriosis, and symptoms may therefore often regress when steroid concentrations are reduced. A recurrence of pelvic pain within 12 months of suspension of medical therapy has been reported (Barbieri, 1991).

Patients with severe pelvic pain should undergo prolonged treatment, but this may not be possible due to side-effects related to low oestrogen levels. In the present study, an attempt was made to obviate these problems by administering low doses of danazol for 6 months after surgery and GnRH treatment, with the aim of maintaining a degree of suppression of the implants. Serum oestradiol concentrations were <73 pmol/l during GnRH therapy and returned to values >180 pmol/l in all women, including those with oligomenorrhoea. This concentration is above the oestrogen threshold of 147 pmol/l.

It is well known that a premenopausal decrease in bone mass is associated with an increased risk of postmenopausal osteoporosis. Hypo-oestrogenism in fertile women caused by GnRH agonists is probably due not only to the effect of oestrogen concentrations within normal limits and increases BMD. This is well shown tended to be the reverse (Jones et al., 1995).

Figure 3. Mean visual analogue score of pain in group A (14 patients treated with 100 mg/day danazol) and group B (14 control patients). After surgery but before GnRH therapy, after GnRH therapy (6 months) and 12 months (after danazol therapy in the case of group A) and 24 months after surgery. Group A and group B values are significantly different (+ P < 0.01; * P < 0.05, Student’s t-test).

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