Effects of 3 month therapy with danazol after laparoscopic surgery for stage III/IV endometriosis: a randomized study

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The effect of treatment with danazol was evaluated with respect to expectant management after laparoscopic conservative surgery. All patients conservatively operated at laparoscopy for stage III–IV endometriosis from July 1994 to October 1996 were requested to enter the study. Patients who underwent surgery for recurrent endometriosis were excluded from the study, as well as patients who had taken hormonal therapies before laparoscopy. Informed consent was obtained from 77 women who were randomized after surgery to treatment with danazol 600 mg daily for 3 months (n = 36) or to expectant management (n = 41). All patients were regularly followed up every 6 months for evaluation of fertility, recurrence of pain symptoms and disease. During the follow-up, six (55%) of the 11 infertile women allocated to danazol and eight (50%) of the 16 given no treatment became pregnant (not significant). Moderate/severe pelvic pain recurred during follow-up in seven (23%) of the 31 women with pelvic pain allocated to the danazol group and nine (31%) of the 29 allocated to no treatment; the respective cumulative pain recurrence rates at 12 months were 26 and 34% (log rank test, not significant). Three women (8.3%) treated with danazol and six (15%) who received no treatment had disease recurrence as demonstrated by gynaecological examination and/or pelvic ultrasonography (not significant). Our results do not demonstrate a significant advantage of 3 month danazol therapy after laparoscopic surgery for stage III–IV endometriosis with respect to postoperative expectant management. Key words: danazol/endometriosis/laparoscopy

Introduction

Combined surgery and medical therapy represents the best treatment for endometriosis according to various authors (Wheeler and Malinak, 1981; Daniell and Christianson, 1981; Buttram et al., 1982; Chong, 1985; Buttram, 1990; Thomas, 1992; Malinak, 1993; Muzii et al., 1996; Rana et al., 1996). Theoretically, postoperative medical treatment may eradicate any foci of endometriosis remaining after surgery and this improves the results of the procedure. It may also stop the implantation and growth of endometriotic tissue disseminated at surgery and prevent recurrence.

However, there are so few clinical trials that address this question that it is impossible to draw any conclusions from the literature. In particular, clinical studies are lacking on hormonal treatment after laparoscopic surgery for endometriosis. Operative laparoscopy is now considered the most appropriate surgical approach to all stages of endometriosis (Cook and Rock, 1991; Bateman et al., 1994), with a few noteworthy exceptions (Crosignani et al., 1996).

We designed a randomized clinical trial to investigate the efficacy of postsurgical treatment with danazol in women with stage III or IV endometriosis.

Materials and methods

A total of 77 women entered the study. Inclusion criteria were ≤40 years old with unexplained infertility and/or chronic pelvic pain, and laparoscopic surgery undertaken for moderate or severe endometriosis according to the revised American Fertility Society (r-AFS) classification (American Fertility Society, 1985). Informed consent was obtained from all patients before study entry.

Women who had previously undergone medical or surgical treatment for endometriosis or had other diseases that might affect fertility or cause pelvic pain were excluded, as were women without pain symptoms and not desiring children and those with liver or endocrine disease. The laparoscopic procedures were performed according to the technique described by Cook and Rock (1991).

Randomization was done within 7 days of surgery according to a computer-generated list. Thirty-six patients were randomized to treatment with danazol 600 mg/day for 3 months after surgery and 41 patients were allocated to receive no postoperative treatment. The danazol treatment began on day 1 or 2 of the first menstrual flow after surgery.

To evaluate variations in pain symptoms, subjects with moderate or severe symptoms were investigated before surgery. Before operation all the women completed a questionnaire on the presence and severity of dysmenorrhoea and pelvic pain, and the presence of deep dyspareunia (Fedele et al., 1993). The severity of dysmenorrhoea and pelvic pain was evaluated according to two scales. One was multidimensional and considered any limitation of daily activities, the coexistence of systemic symptoms and the need for analgesics. On the other linear scale, pain severity was scored from 0 to 10, with 0 indicating the absence of pain, and scores of 1–4, 5–7 and 8–10 indicating mild, moderate and severe pain respectively.

All infertile women underwent a standard diagnostic work-up before the operation, including hysterosalpingography, hormone profile (two follicle-stimulating hormone, luteinizing hormone and oestradiol assays in the follicular phase and three progesterone and prolactin assays in the luteal phase), and postcoital test. Furthermore, all partners had two semen analyses.

Every 6 months the patients underwent a standard gynaecological
Table I. Characteristics of patients

<table>
<thead>
<tr>
<th></th>
<th>Danazol (n = 36)</th>
<th>No treatment (n = 41)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;30</td>
<td>19 (53)</td>
<td>19 (46)</td>
</tr>
<tr>
<td>≥30</td>
<td>17 (47)</td>
<td>22 (54)</td>
</tr>
<tr>
<td>Stage of endometriosis&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>29 (80)</td>
<td>36 (88)</td>
</tr>
<tr>
<td>IV</td>
<td>7 (20)</td>
<td>5 (12)</td>
</tr>
<tr>
<td>Infertility</td>
<td>11 (31)</td>
<td>16 (39)</td>
</tr>
<tr>
<td>Pelvic pain</td>
<td>31 (86)</td>
<td>29 (79)</td>
</tr>
</tbody>
</table>

Values in parentheses are percentages.  
<sup>a</sup>According to American Fertility Society (1985) revised classification.

Results

Table I shows the age, stage of endometriosis, infertility and pelvic pain of the patients according to treatment. The distribution of these variables was similar in the two groups. Two women given danazol (5.5%) and three who received no treatment (7.3%) had macroscopically residual endometriosis at the end of laparoscopic surgery (not significant).

No patient was lost to follow-up, which ranged from 6–36 months. During danazol treatment six women (16.7%) experienced symptoms of hyperandrogenism (seborrhoea and acne) and three (8.3%) had a weight gain ≥3 kg.

During the follow-up, six (55%) of the 11 infertile women allocated to danazol and eight (50%) of the 16 given no treatment became pregnant (not significant); the respective cumulative pregnancy rates at 12 months were 59 and 53% (log rank test, not significant). Moderate/severe pelvic pain recurred during the follow-up in seven (23%) of the 31 women with pelvic pain allocated to the danazol group and nine (31%) of the 29 allocated to no treatment; the respective cumulative pain recurrence rates at 12 months were 26 and 34% (log rank test, not significant).

Three women (8.3%) treated with danazol and six (15%) who received no treatment had disease recurrence as demonstrated by gynaecological examination and/or pelvic ultrasonography (not significant).

Only one patient, allocated to the no-treatment group, was re-operated on, and the diagnosis of endometriosis was confirmed at histological examination.

Discussion

The results of our trial suggest that a 3 month course of danazol after operative laparoscopy in women with stage III/IV endometriosis does not confer significant additional benefit.

Potential bias should be taken into account. Our trial was not blind, and we did not use placebo. However, it is difficult to conduct a true blind trial considering the frequent side-effects and the occurrence of amenorrhoea during danazol treatment.

Our sample size was relatively small and we cannot exclude with certainty differences smaller than those observed in the pain control and reproductive performance. In particular, it was not easy identifying a difference in the reproductive outcome between the two groups because of the relatively few infertile women included in the trial. On the other hand, with this sample size we could exclude, at the usual level of study power (β = 0.20), a two-fold lower pain recurrence rate in the danazol-treated versus the untreated women. Other sources of bias can be excluded as all patients were regularly monitored, compliance with the study protocol was complete, and the two groups were comparable in terms of age, reproductive history, pain symptoms and disease stage.

The present findings should be discussed in relation to the available published data. The pain recurrence rates and the pregnancy rates observed in our two study groups are comparable to those reported in the largest reviews of the literature (Hughes et al., 1993; Adamson and Pasta, 1994; Candiani et al., 1995). Comparison with previous studies on postoperative medical treatment is, however, difficult because of differences in patient characteristics, disease extension and surgical procedures.

Data on recovery of fertility and disease recurrence rates reported in these studies are conflicting (Olive and Haney, 1986; Malinak, 1993), and major shortcomings in design, methodology and analysis make them of uncertain value (Olive and Haney, 1986). After the first large and enthusiastic trial performed by Wheeler and Malinak (1981), results on the use of postoperative danazol have been less positive (Olive and Haney, 1986). The only randomized trial published on postoperative administration of a gonadotrophin releasing hormone agonist did not demonstrate any advantage of a 3 month course of nafarelin over placebo in reducing pain recurrence and improving reproductive performance (Parazzini et al., 1994).
Postoperative danazol therapy for endometriosis

coelomic metaplasia, are not definitively eliminated either by surgery or by hormonal therapies.

If postoperative medical therapy yields no benefits, then we must consider the problems associated with its use: it is expensive, has systemic side-effects and may delay the recovery of fertility.

In conclusion, a 3 month course of danazol after laparoscopic surgery for stage III/IV endometriosis does not markedly improve the short-term reproductive prognosis or pelvic pain. A larger series and longer follow-up are, however, required to identify less marked effects of treatment, in particular on the disease recurrence rate.

References