A gonadotrophin-releasing hormone agonist compared with expectant management after conservative surgery for symptomatic endometriosis

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Objective To ascertain whether the frequency of pelvic pain recurrence is reduced and time to symptoms recurrence is prolonged in women with symptomatic endometriosis undergoing conservative surgery and post-operative hormonal therapy compared with women treated with surgery only. Pregnancy rates and time to conception in women wanting children were also evaluated.

Design A multicentre, prospective, randomised controlled study.

Setting Nineteen Italian academic departments and teaching hospitals specialising in reparative and reconstructive surgery.

Population A total of 269 women undergoing conservative surgery for mild to severe symptomatic endometriosis.

Methods After surgery the women were assigned to treatment with subcutaneous goserelin depot injections for six months or to expectant management. Dysmenorrhoea, deep dyspareunia, nonmenstrual pain and general discomfort were graded according to a verbal rating scale from 0 (absent) to 3 (severe) and the scores summed to give a total symptoms score. Only patients with at least one preoperative moderate or severe symptom were enrolled. The women were evaluated regularly for two years.

Main outcome measures Post-operative pain recurrences (total symptoms scores ≥ 5), time to recurrence, pregnancy rates and time to conception in the two study groups.

Results At one- and two-year follow up visits, 14/107 (13.1%) and 19/81 (23.5%) patients had moderate or severe symptoms recurrence in the goserelin group compared with, respectively, 22/103 (21.4%) and 27/74 (36.5%) in the expectant management group (P = 0.143 at 1 year and 0.082 at 2 years). Time to symptoms recurrence was significantly longer in the goserelin group according to survival analysis (Wilcoxon test, P = 0.041). Among women wanting children, few conceptions occurred in both the goserelin (8/69, 11.6%) and the expectant management group (14/76, 18.4%). There was no significant difference at survival analysis (Wilcoxon test, P = 0.427).

Conclusion Post-operative treatment with goserelin significantly prolonged the pain-free interval after conservative surgery for symptomatic endometriosis and did not influence reproductive prognosis.

INTRODUCTION

Conservative surgery at laparoscopy or laparotomy is frequently the treatment of choice for symptomatic endometriosis, especially in its advanced forms. However, results are often disappointing and disease recurrence is common. Hypo-oestrogenising medical treatment after conservative surgery may sterilise microscopic foci, induce resorption of lesions that could not be removed and reduce the risk of iatrogenic dissemination of endometriotic cells. This should improve post-operative pain relief and pregnancy rates, but there is no consensus on this and the limited information available from small randomised controlled trials is...
This open-label, parallel-group, randomised controlled trial compared treatment with a GnRH agonist for six months after conservative surgery for endometriosis with post-operative expectant management. The women gave written, informed consent, and the protocol was approved by independent ethics committees of the institutions involved.

Premenopausal women with chronic pelvic pain who underwent conservative surgery for endometriosis at laparoscopy or laparotomy at the participating centres between February 1992 and June 1994 and who had an endometriosis score of ≥ 4 points according to the revised American Fertility Society classification were considered for recruitment to the study. No specific technique or instrumentation (excision with microsurgical mechanical devices, fulguration with electrosurgery, vaporisation or coagulation with various types of lasers) was deemed essential for inclusion. The women were asked to grade the degree of their pre-operative pain symptoms according to the 0 to 3-point verbal rating scale devised by Biberoglu and Behrman which defines:

a. dysmenorrhoea (according to loss of work efficiency and need for bed rest)
   1. mild: some loss of work efficiency;
   2. moderate: in bed part of one day, occasional loss of work;
   3. severe: in bed for 1 or more days, incapacitation
b. nonmenstrual pain (according to degree of discomfort and use of analgesics)
   1. mild: occasional pelvic discomfort;
   2. moderate: noticeable discomfort for most of the cycle;
   3. severe: pain persisting during the cycle or requiring strong analgesics
c. deep dyspareunia (according to limitation of sexual activity)
   1. mild: discomfort tolerated;
   2. moderate: intercourse painful to the point of interruption;
   3. severe: intercourse avoided because of pain.

In addition, general discomfort (occasional, 1; frequent, 2; constant, 3) was also assessed. The scores for each of the four symptoms were added to obtain the total symptoms score. Only women with at least one moderate or severe symptom before surgery (total score ≥ 5) were considered eligible for the trial. Women who were pregnant or breastfeeding, had serious concomitant illnesses, or had been treated with hormonal agents in the previous three months were excluded.

Within one week of conservative surgery and after completion of the pretrial screening, eligible women were randomised in a proportion of 1:1 to treatment with subcutaneous goserelin depot injections (3.6 mg; Zoladex, Zeneca Pharmaceuticals, Macclesfield, UK) on six occasions 28 days apart, or to expectant management. Centralised treatment allocation was performed by telephone in accordance with a computer-generated randomisation sequence, balanced for treatments, produced for each participating centre.

All the women were examined monthly for the first six months after surgery, then every two months for six months, and finally every six months until completion of a two-year follow up period. At each follow up visit a standard gynaecologic examination was performed, the occurrence of pregnancy was recorded, and pain symptoms were assessed according to the 4-point verbal rating scale. Post-operative symptoms recurrence was defined as a total symptoms score of ≥ 5 points. In case of sexual inactivity or refusal of the patient to respond, the score assigned to dyspareunia was the average score of the three other symptoms assessed.

The primary objective in determining sample size was rate of recurrence of symptoms in the two study groups one year after randomisation. According to literature data, the one-year pain recurrence rate in women undergoing conservative surgery alone for symptomatic endometriosis is around 20%. For subjects receiving post-operative GnRH agonist treatment the expected recurrence rate was set at 5%. To have a 90% chance of detecting a 15% reduction at an overall significance level of 5% (two-tailed test), a total of 260 patients would be required, allowing for a 20% drop-out rate. Percentages of patients with symptoms recurrence in the two groups at one- and two-year follow up were compared with Fisher's exact test. The Breslow-Day test was performed to verify homogeneity between centres in terms of percentages, expressed as odd ratios. The 95% limits of confidence intervals for the differences between groups were calculated using the normal approximation to binomial distribution corrected for continuity. In addition, odds ratios with their exact CI were calculated. Time to symptom recurrence and time to conception were analysed with the Kaplan-Meier method and the curves obtained were compared by the Wilcoxon test. The event dates used in computing the
cumulative probability of recurrence of moderate or severe symptoms were the date of surgery and the date of recurrence or last follow up visit or last menstrual period in case of conception. The event dates used in computing the cumulative probability of becoming pregnant were the date of surgery for the expectant management group or 28 days after the last GnRH agonist injection for the goserelin group, and the date of the last menstrual period or last follow up visit.

RESULTS

A total of 269 women were randomised by 19 centres. Two patients and consequently one centre were excluded because the case report forms were not completed, leaving 133 women in the goserelin group and 134 in the expectant management group. The entry characteristics of the two study groups were comparable (Table 1). Fifty-seven women (26 in the goserelin group and 31 in the expectant management group) withdrew after randomisation and before the end of the first year of treatment for reasons other than symptoms recurrence or were excluded from the primary efficacy analysis due to major protocol violations. Among the 210 women evaluable for pain recurrence at one-year follow up, 14/107 (13.1%) had moderate or severe symptoms in the goserelin group, compared with 22/103 (21.4%) in the expectant management group (P = 0.143, Fisher's exact test), with an observed difference of 8.3% in symptoms recurrence rate (95% CI -2.9% to +19.4%; OR 0.55, 95% CI 0.25 to 1.22). Recurrence occurred in four of the 14 goserelin treated patients during the drug administration period. At two-year follow up, 155 women were evaluated. In the goserelin group 19/81 (23.5%) women experienced symptoms recurrence, compared with 27/74 (36.5%) in the expectant management group (P = 0.082, Fisher's exact test), the observed difference in symptoms recurrence rate (95% CI -2.6% to 28.7%; OR 0.53, 95% CI 0.25 to 1.14). In 95/127 (75%) and 77/125 (62%) of the patients who could be evaluated, respectively, in the goserelin and expectant management group the total symptoms score fell to zero during the study period. Nine of the former (9/95, 9.5%) and five of the latter subjects (5/77, 6.5%) subsequently experienced recurrence of symptoms. Dysmenorrhoea, alone or associated with other symptoms, was the most frequent moderate or severe event recorded. The Breslow-Day test for homogeneity of odds ratios among centres did not reveal statistically significant differences ($\chi^2$ at one year = 14.3, df = 12, $P = 0.283$; $\chi^2$ at two years = 12.8, df = 9, $P = 0.172$), although some heterogeneity seemed to be present. In the two centres with the most patients (Milano and Monza) the difference between treatments was close or equal to zero and the rate of recurrence was extremely low. Figure 1 shows survival analysis for the two study groups and the related numbers of subjects at risk over the study period. The median follow up time was 644 days for the goserelin group and 539 days for the expectant management group. The Wilcoxon test demonstrated a statistically significant difference in time to symptoms recurrence in favour of goserelin ($\chi^2 = 4.19$, $P = 0.041$). The cumulative 24-month probabilities of pain recurrence by disease severity in the post-operative medical treatment and surgery only arms were, respectively: 100% and 80% at Stage I; 20% and 48% at Stage II; 13% and 18% at Stage III; and 20% and 23% at Stage IV.

Of the subgroup of 152 women wanting children at the basal visit, 145 could be evaluated with regard to pregnancy rate after treatment during the follow up period. Few conceptions were observed in both the goserelin (8/69, 11.6%) and the expectant management group (14/76, 18.4%), the difference being not significant ($P = 0.354$, Fisher's exact test; OR 0.58, 95% CI 0.23 to 1.48). Time to conception was not significantly different in the two groups as assessed by survival analysis ($\chi^2 = 0.63$, $P = 0.427$; Wilcoxon test (Fig. 2).

DISCUSSION

The aim of medical treatment after conservative surgery for endometriosis is to 'sterilise' microscopic or inaccessible residual pelvic foci and reduce peri-adnexal adhesion formation by avoiding follicular and luteal

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Table 1. Demographic and basal characteristics of women undergoing conservative surgery for endometriosis with or without post-operative gonadotrophin-releasing hormone agonist treatment. Values are given as n (%) or mean [SD].

<table>
<thead>
<tr>
<th>Disease stage*</th>
<th>Goselin group (n = 133)</th>
<th>Control group (n = 134)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>30.1 [5.4]</td>
<td>30.0 [5.3]</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>56.3 [7.8]</td>
<td>56.8 [9.3]</td>
</tr>
<tr>
<td>Total symptoms score†</td>
<td>78 [58-6]</td>
<td>82 [61-2]</td>
</tr>
<tr>
<td>5-6</td>
<td>78 [58-6]</td>
<td>82 [61-2]</td>
</tr>
<tr>
<td>7-8</td>
<td>43 [32-3]</td>
<td>41 [30-6]</td>
</tr>
<tr>
<td>9-10</td>
<td>8 [6-0]</td>
<td>9 [6-7]</td>
</tr>
<tr>
<td>11-12</td>
<td>3 [2-6]</td>
<td>2 [1-5]</td>
</tr>
<tr>
<td>Women wanting children</td>
<td>76 [57-1]</td>
<td>76 [56-7]</td>
</tr>
<tr>
<td>Surgery at laparotomy†</td>
<td>68 [51-1]</td>
<td>64 [47-8]</td>
</tr>
<tr>
<td>Surgery at laparoscopy†</td>
<td>64 [48-1]</td>
<td>70 [52-2]</td>
</tr>
</tbody>
</table>

*According to the revised American Fertility Society classification.
†Description of one case in the goserelin group is missing.

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Fig. 1. Cumulative 24-month probability of moderate or severe symptoms recurrence as assessed by a verbal rating scale in 267 women undergoing conservative surgery for symptomatic endometriosis according to post-operative treatment: (dotted line) goserelin (n = 133); (solid line) expectant management (n = 134) (Wilcoxon test, $\chi^2 = 4.19, P = 0.041$). Vertical tick marks represent censored observations.

Fig. 2. Cumulative 24-month probability of becoming pregnant in 145 women wanting children undergoing conservative surgery for symptomatic endometriosis according to post-operative treatment: (dotted line) goserelin (n = 69); (solid line) expectant management (n = 76) (Wilcoxon test, $\chi^2 = 0.63, P = 0.427$). Vertical tick marks represent censored observations.
activity during ovarian healing. Three randomised controlled trials have been published on this topic by survival analysis. In other words, the pain-free interval are similar in the two study groups, the comparison was significantly prolonged in the goserelin group rates one year after surgery between 36 women allocated to post-operative intranasal nafarelin 400 mg/day for three months and 39 women receiving placebo nasal spray. Recently Hornstein et al. administered the same GnRH agonist at the same daily dosage for six months after reductive laparoscopic surgery for symptomatic endometriosis, and found that 15 of 49 women treated with nafarelin (31%) required an alternative therapy for recurrent pain compared with 25 of 44 women (57%) allocated to post-operative placebo. Furthermore, the median time to institution of alternative treatment was significantly longer in the former group.

A limitation of our study is the open-label design. A double-blind, placebo-controlled trial would have been preferable, but we considered it difficult to conduct a true blind study because of the frequent side effects observed during a six-month treatment with GnRH agonists, chiefly amenorrhoea and hot flushes. Patients were operated either at laparotomy or laparoscopy, but this should not bias the results, given the randomised assignment. We adopted centralised phone randomisation to ensure allocation concealment. Furthermore, there is no evidence that the type of surgery influences long term outcomes in terms of pain recurrence and pregnancy rates.

No statistically significant difference between the study arms was found in symptomatic recurrence rate at one year. The frequency for the expectant management group was fully consistent with that expected (21-4% vs 20%), but the estimated rate difference compared with the goserelin group, although still consistent, was lower than expected (8-3% vs 15%). Similar non-statistically significant results were observed at the two-year comparison. Because the crude rate of symptoms recurrence was calculated excluding not only patients with major violations or deviations but also those withdrawn from the study in the first year, the true rate could be underestimated. However, considering that both the number of patients withdrawn and the length of the observation period are similar in the two study groups, the comparison should be unbiased. A significant treatment effect was observed in time to symptoms recurrence assessed by survival analysis. In other words, the pain-free interval was significantly prolonged in the goserelin group compared with the expectant management group.

No significant differences were found between the two groups in time to conception and in pregnancy rates (11-6% versus 18-4%), which were, in general, lower than those reported after surgery alone, medical therapy or combined treatment. As only some of the recruited women tried to become pregnant, the power of our study to detect a clinically important difference in conception rates is admittedly limited. Interestingly, also Telimaa et al. and Parazzini et al. observed low pregnancy rates in their trials. In the latter study, only 7/36 (19%) women in the nafarelin arm and 7/39 (18%) in the placebo arm achieved a pregnancy within one year of surgery. For the goserelin group we computed data for survival analysis expressing time to conception relative to the end of medical treatment rather than time of surgery, because anovulation induced by GnRH agonists renders pregnancy highly improbable. In the opinion of some experts the post-operative period is particularly favourable for conception and suppressing ovulation for some months after surgery may be detrimental in the case of infertile women. Neither our data nor those in the literature definitively disentangle this issue.

In conclusion, the results of this study suggest that treatment with goserelin after conservative surgery for endometriosis significantly delays the reappearance of pelvic pain symptoms and does not influence reproductive prognosis.

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