Successful treatment of refractory endometriosis-related chronic pelvic pain with aromatase inhibitors in premenopausal patients

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A B S T R A C T

Objective: Not every patient with endometriosis responds to currently recommended conventional medical treatment regimens. The objective of this study was to determine the efficacy and side effects of aromatase inhibitors in the treatment of premenopausal patients with endometriosis associated with chronic pelvic pain refractory to conventional treatment.

Study design: Four premenopausal patients with documented refractory endometriosis and chronic pelvic pain were treated with aromatase inhibitors, either anastrazole (3) or letrozole (1), for 6 months. The treatment was combined with calcium 1.5 g per day and vitamin D 800 U per day. The main outcome measure was reduction in pelvic pain assessed by visual analogue scale. Side effects were documented and changes in serum LH, FSH and 17-ß estradiol and bone density (Dexa scan) were measured before, during and after treatment.

Results: There was marked improvement in pelvic pain in the four patients. Their mean pain score fell from 9 prior to treatment to 4.5 at the end of treatment. One patient with infertility conceived immediately after completing the treatment. There were no changes in the hormone levels and bone scan scores. The most common side effect was irregular bleeding with anastrazole and joint pains with letrozole.

Conclusions: Aromatase inhibitors are beneficial in premenopausal women with chronic pelvic pain secondary to refractory endometriosis without compromising fertility and with minimal side effects. Further cohort and comparative studies are needed to confirm these observations.


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1. Introduction

Endometriosis is an estrogen-dependent disease characterized by the presence of functional endometrial tissue outside the uterus. It is an important cause of long-term morbidity, commonly from chronic pelvic pain and infertility. It affects approximately 71–87% of premenopausal women with chronic pelvic pain [1]. The goal of current medical treatment (e.g. combined oral contraceptives, Depo-Provera, oral progestins, danazol and GnRH agonists) is either to induce hypo-estrogenism or antagonize estrogen action. Masculinizing side effects of danazol along with the reported increase in baseline risk of ovarian cancer have essentially rendered its use obsolete [2]. GnRH agonists are used for short term only in view of the risk of osteopenia. Surgical methods while effective either in the short, medium or long term are not appropriate to all patients or fail to provide symptom relief in others. Recently, aromatase inhibitors have been proposed as novel potential candidates for treatment of endometriosis. Aromatase is a key enzyme in the synthesis of estrogens. It mediates the conversion of androstenedione and testosterone to estrogens. High aromatase expression in endometriotic cysts/extra-ovarian endometriotic implants resulting in local production of estrogens accounts for failure of conventional medical treatment. It is on this basis that aromatase inhibitors have been proposed for the treatment of endometriosis-related pelvic pain refractory to conventional treatment.

There is presently one case report documenting successful treatment of refractory endometriosis with the use of anastrazole, progesterone, calcitrol and rofecoxib [3]. There is also a prospective open-label phase 2 trial reporting significant pain relief with the use of anastrozole and oral contraceptive [1]. Progesterone and oral contraceptive pill are used in the treatment of endometriosis and hence may have synergistic effect when used with anastrozole. We present four cases of premenopausal women with refractory endometriosis successfully treated with aromatase inhibitors, alendronate, calcium and vitamin D.
2. Materials and methods

Four premenopausal patients with documented endometriosis-related chronic pelvic pain that was refractory to conventional treatment were offered treatment with aromatase inhibitors. The eligibility criteria were age 25–40 years, confirmed endometriosis and persisting pelvic pain refractory to medical and surgical treatment. Those with clinical or radiological evidence of osteoporosis, severe renal impairment, liver disease or abnormal liver function tests, abnormality of the oesophagus, conditions which delayed bowel emptying, and hypocalcaemia, were excluded.

Consent for the treatment was obtained from each patient after a thorough explanation to the effect that

(a) the treatment was novel with very limited data in the literature and

(b) side effects may include hot flushes, asthenia, joint pains/stiffness, rash, nausea, diarrhoea and headache.

The treatment phase consisted of either anastrozole 1 mg once daily (OD) with alendronate 10 mg OD or letrozole 2.5 mg OD with norethisterone acetate 2.5 mg daily. For either option calcium 1.5 g per day and vitamin D 800 U per day were given for total duration of treatment (6 months).

Prior to commencing treatment, baseline serum urea and electrolytes, kidney and liver function tests, and serum hormonal levels (FSH, LH and estradiol) were performed. These were repeated monthly during and 1 month after completion of treatment. Additionally bone densitometry of the hip and lumbar levels (FSH, LH and estradiol) were performed. These were repeated monthly during and 1 month after completion of treatment. T-score values representing differences in bone mass densities relative to a standard young adult women’s mean value were expressed as standard deviations (S.D.).

The patients were followed up at 1, 4 and 6 months after the commencement of treatment and 3–4 months after completion. At each follow-up visit the side effects were documented and changes in pain score were assessed on a visual analogue scale (VAS) of 0–10 scales (where 0 = no pain and 10 = most severe pain) [4,5].

3. Results

Table 1 summarizes the patient characteristics and prior medical and/or surgical interventions. Three of the four had had a combination of surgical and medical treatment while one only had medical treatment.

All four patients had either failed or partially responded to multiple prior treatments. Three of these patients had moderate to severe endometriosis (stage 3 or 4 based on the revised American Society for Reproductive Medicine Endometriosis Scoring System-1985) [6]. Cases 1–3 were nulliparous and case 3 had associated infertility. Case 2 had been referred at the age of 20 years with a request for hysterectomy as she could not cope with pain and all medical options tried had failed.

Cases 1–3 were started on anastrozole and case 4 on letrozole for a period of 6 months. Case 1 reported improvement in pain within 6 weeks of starting treatment. (Her pain score fell from 10 to 2 and stayed at 2 until the end of treatment.) Her pain score however increased to 5 within 3 weeks of completing the 6 months course and she requested to restart the treatment, as she was worried her pain would worsen.

Case 2 also reported improvement in pain 4 weeks into her treatment although her pain score only fell from 8 to 6.5. She reported a marked improvement in the effects of pelvic pain on her life as she was now able to cope and used less analgesia. She completed her 6 months treatment but then moved away and could not attend her follow-up bone densitometry. She was given the option to re-attend if symptoms re-occurred by 6 months after completing the treatment but she has not returned.

The pain score of case 3 fell from 8.5 to 4.5. She completed 6 months of treatment and became pregnant soon after completing the course of anastrozole. She has subsequently had an uneventful pregnancy and delivered a normal male infant at term that weighed 3.685 kg.

Case 4 was started on letrozole after baseline investigations. By the end of the first month she started noticing improvement in pain but also had significant side effects in the form of joint pains. Her norethisterone dose was increased to 5 mg per day. By the end of 6 months her visual analogue pain score had reduced from 9.5 to 5. Her pains were restricted to mainly prior to periods. Increasing the dose of norethisterone did not make any significant difference.

All patients showed a significant improvement in pain by the end of treatment. Table 2 summarizes the pain scores of the four patients.

Table 2

<table>
<thead>
<tr>
<th></th>
<th>Pretreatment pain score</th>
<th>Pain score at completion of 6 months treatment</th>
<th>Pain score 3 months after completion of treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case 1</td>
<td>9.5</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Case 2</td>
<td>8</td>
<td>6.5</td>
<td>NA</td>
</tr>
<tr>
<td>Case 3</td>
<td>8.5</td>
<td>4.5</td>
<td>7.5</td>
</tr>
<tr>
<td>Case 4</td>
<td>9.5</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Mean ± S.D.</td>
<td>8.8 ± 4.5</td>
<td>4.5 ± 1.5</td>
<td>4.5 ± 1.5</td>
</tr>
</tbody>
</table>

Table 1

Characteristics of the four patients treated with aromatase inhibitors.

<table>
<thead>
<tr>
<th></th>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
<th>Case 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>35</td>
<td>23</td>
<td>33</td>
<td>35</td>
</tr>
<tr>
<td>Parity</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Site of endometriosis</td>
<td>Ovarian endometrioma</td>
<td>Endometriotic nodules in pouch of Douglas and on bowel adhesions</td>
<td>Rectovaginal endometriosis</td>
<td>Ovarian endometriosis</td>
</tr>
<tr>
<td>Symptoms</td>
<td>Pelvic pain, constipation, apareunia</td>
<td>Pelvic pain, dyspareunia</td>
<td>Pelvic pain, dyspareunia (severe), infertility</td>
<td>Pelvic pain, dyspareunia</td>
</tr>
<tr>
<td>Previous surgery</td>
<td>Diagnostic laparoscopy (10×*), laser treatment of endometriosis, laparoscopic assisted vaginal hysterectomy</td>
<td>Helium beam coagulation of endometriosis, laparoscopic uterine nerve ablation, laparoscopic adhesiolysis and laser excision</td>
<td>Ovarian cystectomy, laser adhesiolysis (2×*)</td>
<td>Diagnostic laparoscopy, declined further surgery involving oophorectomy</td>
</tr>
</tbody>
</table>

* Number of times this treatment was offered.
There were no changes in FSH, LH and 17-β estradiol levels before, during and after treatment with aromatase inhibitors. Fig. 1 shows that the treatment did not have any significant effect on bone densitometry. The main side effect with anastrazole was irregular bleeding which the patients considered as minimal and tolerated it well. The patient on letrozole reported significant joint pains, but persisted with the treatment till completion as it had significantly improved her symptoms. Her bone profile and Dexa scan remained normal throughout treatment. These pains stopped when she completed treatment and her chronic pelvic pain remains resolved.

4. Comment

Approximately half of patients with chronic pain associated with endometriosis are refractory to currently available conventional medical treatments which are designed to decrease estrogen secretion by ovaries [7]. A possible reason for this is the local estrogens synthesised by the aberrant expression of aromatase enzyme in endometriotic lesions, which escapes the effects of conventional treatment. Moreover peripheral estrogen production from adipose tissue and skin is not affected by conventional medical treatment.

Aromatase inhibitors, by affecting these additional sites, are therefore a potential therapeutic option for refractory endometriosis. They are classified into two types—type I inhibitors (suicidal or noncompetitive) and type II inhibitors (competitive). Anastrazole and letrozole are third generation type II inhibitors.

Takayama et al. [3] reported the first case of successful treatment of refractory endometriosis in a postmenopausal woman with the aromatase inhibitor anastrazole who had undergone a hysterectomy and bilateral salpingo-oophorectomy. Not only was there a significant improvement in symptoms; the size of endometriotic lesion reduced and levels of aromatase P450 mRNA fell. In 2004, Razzi et al. reported a case of a premenopausal woman with recurrent pelvic pain due to endometriosis, which re-occurred after a subtotal hysterectomy and bilateral ovariectomy. She was treated with the aromatase inhibitor, letrozole, with marked improvement in the symptoms [8]. A major concern with this treatment is the generalized hypoestrogenic state that it induces. This was not the case in our small series.

The aromatase inhibitors inhibit estrogen production in at least four critical body sites—the brain, ovary, endometriosis and periphery (adipose tissue and skin) [7]. Of these, granulosa cells in the ovary have huge amount of aromatase levels. Studies in premenopausal women with breast carcinoma have shown partial inhibition of ovarian estrogen levels with use of aromatase inhibitors [9]. It may be because of overwhelming levels of aromatase in granulosa cells [7] or because of reflex increment of LH and FSH that aromatase inhibitors become ineffective. Early studies that have examined estrogen levels in premenopausal women with breast cancer treated with aromatase inhibitors have shown elevated gonadotrophin concentrations [9,10]. It is possible that elevated gonadotrophins might negate the benefits of the treatment by increasing ovarian estrogen production. To overcome this Shippen and William (2004) added oral progesterone (200 mg) daily to the treatment regimen to reduce LH and FSH activity by direct inhibition. Additionally rofecoxib 12.5 mg daily (a long acting COX2 pathway inhibitor) was included to reduce proinflammatory COX2 metabolites in endometriotic implants, which are known to increase both endogenous stimulation of aromatase and symptoms of disease [11]. This regimen was used in two premenopausal patients with good results and minimal side effects.

Another modification to minimise side effects combined anastrazole and the combined oral pill in 19 patients [1].
a total of 19 patients studied, 15 completed 6 months of treatment with minimal side effects; 14 of these reported significant improvement in their symptoms. A randomized control trial by Soysal et al. [12] evaluated the efficacy of either a combination of anastrozole and goserelin for 6 months or goserelin alone for 6 months after conservative surgery for severe endometriosis. They observed an increased pain-free interval and a decreased recurrence of symptoms but a significantly greater bone mineral density loss at the end of treatment in the goserelin and anastrozole arm.

A pilot study using letrozole and norethindrone acetate in 10 premenopausal patients with refractory endometriosis reported marked reduction in pain and laparoscopically visible and histologically confirmed endometriosis [13].

Our study using aromatase inhibitors for 6 months showed reduction in pain scores with minimal side effects. We did not use progesterone with anastrozole and did not observe any LH and FSH surges. Ailawadi et al. [13] did not observe any significant alteration in serum gonadotrophins and estrogens in their study using letrozole (2.5 mg) and norethindrone acetate. We used norethisterone acetate in the dose of 2.5 mg per day along with letrozole as an add back to reduce irregular bleeding. This dose is much less than that recommended dose for endometriosis treatment, but may be synergistic to its response. Although our numbers are small, we achieved pain relief with the use of anastrozole alone with minimal side effects in premenopausal women. So far all other studies have used an adjunctive therapy to suppress ovarian activity in the treatment of premenopausal women with endometriosis. Our results suggest that such treatment may not be necessary. In view of these promising results more studies are required using aromatase inhibitors to establish their role in the treatment of endometriosis and establish which one is best as they have different mechanisms of action and different levels of estrogen suppression [14].

References