LEADING ARTICLE

Drugs 2009; 69 (8): 943-952
0012-6667/09/0008-0943/$55.55/0

Pharmacological Treatment of Endometriosis

Experience with Aromatase Inhibitors

Simone Ferrero,[1] *Pier L. Venturini*,[2] *Nicola Ragni*,[1] *Giovanni Camerini*[3] and *Valentino Remorgida*[1]

1 Department of Obstetrics and Gynecology, San Martino Hospital and University of Genoa, Genoa, Italy
2 Department of Obstetrics and Gynecology, G. Gaslini Institute, Genoa, Italy
3 Department of Surgery, San Martino Hospital and University of Genoa, Genoa, Italy

Abstract

Current treatment of endometriosis is mainly based on surgery and ovarian suppressive agents. In the last 10 years, it has been demonstrated that aromatase P450, a key enzyme for estrogen biosynthesis, may have a pathogenic role in endometriosis because it is aberrantly expressed in endometriotic implants and in eutopic endometrium of women with endometriosis. Therefore, inhibition of aromatase activity may represent a new therapeutic option for endometriosis. Case reports and observational studies have shown that pain symptoms caused by endometriosis quickly improve after administration of aromatase inhibitors. Limited data are available on the long-term course of pain symptoms after completion of treatment with aromatase inhibitors; however, some recent studies suggest that symptoms may recur at short-term follow-up. A range of results are reported on the effects of aromatase inhibitors on endometriotic lesions, with some authors describing improvements and other authors reporting persistence of pelvic lesions at second-look laparoscopy after treatment. No severe adverse effect has been reported during treatment with aromatase inhibitors both in pre- and postmenopausal women. On the basis of the available data, administration of aromatase inhibitors should now be offered only to the small number of women who have severe pain despite previous surgical and hormonal therapies. Further research in the form of randomized controlled trials will be required before recommending the routine use of these agents.

Endometriosis is a benign, estrogen-dependent, gynaecological disorder associated with pelvic pain and infertility. It is defined as the presence of endometrial glands and stroma outside the uterine cavity. Endometriotic lesions may have various locations; they are more frequent on the pelvic peritoneum, on the ovaries, in the rectovaginal septum, on the uterosacral ligaments, and less common in the bowel, bladder, ureters, diaphragm, pleura and lungs. Endometriosis is primarily a disease of the reproductive years and it is only rarely observed in teenage girls and postmenopausal women. The diagnosis is based on surgical visualization of the disease;[1] this criterion has hampered epidemiological investigations aimed at estimating the true prevalence of the

disease in women without specific pathology. Prospective studies documented a prevalence of endometriosis of 4–19% in women undergoing laparoscopic tubal sterilization; however, it is more frequent in women undergoing surgery because of pain symptoms or infertility (10–47%).[2,3]

Pain represents the major clinical problem of women with endometriosis; these patients may present with dysmenorrhoea, dyspareunia, chronic pelvic pain and dyschezia. In addition, women with endometriosis may experience infertility; however, the mechanisms by which endometriosis causes infertility are still largely not well defined. Despite a long history of clinical experience and experimental research, endometriosis remains an enigma and its pathogenesis is still controversial. The most widely accepted theory on the pathogenesis of endometriosis is Sampson's theory proposing that the disorder originates from retrograde menstruation of viable endometrial tissue through the fallopian tubes into the peritoneal cavity where it implants on the peritoneal surface or pelvic organs.[4] This theory is supported by the following three observations: (i) endometrial cells enter the peritoneal cavity through the fallopian tubes; (ii) refluxed endometrial cells are viable in the peritoneal cavity; and (iii) refluxed endometrial cells can adhere to the peritoneum and proliferate. However, retrograde menstruation is a common event in almost all cycling women[5] and, therefore, it remains unclear why all women do not develop endometriosis.

Immunological abnormalities that are present in women with endometriosis may contribute to the development and persistence of the disease. Several studies have shown that macrophages present in peritoneal fluid of women with endometriosis are hyperactivated and that they secrete cytokines and growth factors.[6] Ovarian hormones not only have direct effects on endometrial and endometriotic tissue, but they also have indirect effects on endometriosis through the inflammatory cells present in the peritoneal cavity. Estrogen receptors-α and -β are over-expressed in macrophages of women with endometriosis when compared with controls.[7] Furthermore, there is a correlation between the expression of estrogen receptor-β and proinflammatory cytokines (interleukin [IL]-1β, tumour necrosis factor-α, IL-6) on peritoneal fluid macrophages both in women with and without endometriosis; however, the expression of estrogen receptor-α correlates with cytokine production selectively in women with endometriosis but not in controls.[8] These interactions between steroid hormones and peritoneal fluid macrophages suggest that estrogen may promote the progression of endometriosis by acting on the immune system.

1. Principles of Pharmacological Treatment of Endometriosis

The aim of medical therapy for endometriosis is to relieve pain symptoms. Surgical excision of endometriosis significantly improves pain symptoms and quality of life, particularly for women with more severe endometriosis; however, the disease can be chronic and may relapse at short-[9] or long-term follow-up.[10,11] Based on this, pharmacological therapy is used to prevent the recurrence of pain symptoms[12] and ovarian endometriosis.[13] In addition, pharmacological therapy may be used as an alternative to surgery in patients without extensive disease. Pharmacological therapy is rarely offered to women wishing to conceive; in fact, there is no evidence that pharmacological treatment may improve fertility. A further disadvantage for women desiring pregnancy in the near term is that conception is generally not possible during pharmacological therapy; indeed, many of these agents are also used as effective contraceptives.

2. Pharmacological Therapies for Endometriosis

Table I lists the pharmacological therapies commonly used for endometriosis. NSAIDs do not treat endometriotic lesions but they may be effective in reducing the intensity of pain symptoms. Only one randomized controlled trial of naproxen compared with placebo was included in a recent meta-analysis of NSAIDs;[14] this trial did not show a beneficial effect of treatment on pain relief (odds ratio 3.27; 95% CI 0.61, 17.69). However, NSAIDs are often used in women with

Table I. Pharmacological therapies for endometriosis

Category	Agents
NSAIDs	Ibuprofen Naproxen Mefenamic acid
Contraceptives	Oral contraceptives Contraceptive patch Contraceptive ring
Progestogens	Derivatives of progesterone: medroxyprogesterone megestrol dydrogesterone Derivatives of 19-nortestosterone: norethisterone (norethindrone) norgestrel lynestrenol levonorgestrel etonogestrel
Gonadotropin-releasing hormone stimulants	Leuprorelin (leuprolide) Nafarelin Buserelin Goserelin
Gestrinone	
Danazol	

endometriosis with variable outcomes. The oral contraceptive pill is the most commonly used first-line treatment of endometriosis-associated pain and it may also be used empirically. The long cycle and continuous use of oral contraceptives may be preferable in women with endometriosis. Progestogens have for a long time been used continuously to achieve cycle suppression in women with endometriosis. Medroxyprogesterone is effective in relieving pain symptoms and can be administered either orally, intramuscularly or subcutaneously.[15-17] Possible adverse effects include water retention, weight gain and irregular vaginal bleeding. More recently, the levonorgestrel-releasing intrauterine system (Mirena®) has been shown to significantly reduce dysmenorrhoea in women with endometriosis.[18,19] Gonadotropin releasing hormone (GnRH) analogues or stimulants have been widely used in the treatment of severe endometriosis. Placebo-controlled studies reported a significant reduction in the intensity of dysmenorrhoea and chronic pelvic pain of women treated with GnRH stimulant therapy compared with placebo.[20,21] GnRH stimulants are often administered with add-back hormone replacement therapy to minimize their hypoestrogenic adverse effects without apparent reduction in efficacy.

In the last 20 years, our understanding of the pathogenesis of endometriosis at the cellular and molecular level has improved. On the basis of this, several new drugs have been proposed for the treatment of endometriosis. These agents include progesterone antagonists (mifepristone, onapristone, selective progesterone receptor modulators), immunomodulatory agents (pentoxifylline, loxoribine, interferon α-2b, tumour necrosis factor inhibitors), angiogenesis inhibitors, matrix metalloproteinase inhibitors, estrogen receptor-β agonists, selective estrogen receptor modulators and hypocholesterolaemic agents.[22,23]

3. Aromatase P450 in Endometriosis

Aromatase P450 is a key enzyme for estrogen biosynthesis, catalyzing the conversion of androstenedione and testosterone to estrone and estradiol. Androstenedione of adrenal origin is the major substrate for aromatase in peripheral tissues. Estrone, the product of the enzymatic reaction catalyzed by aromatase from androstenedione, is weakly estrogenic and requires conversion to estradiol by the enzyme 17βhydroxysteroid dehydrogenase to attain full estrogenic potency. Aromatase activity is not detectable in the endometrium of healthy women;[24,25] however, this enzyme is expressed in endometriotic implants and in eutopic endometrium of women with endometriosis.[26,27] Prostaglandin (PG)-E_2 is the most potent inducer of aromatase activity in endometriotic stromal cells.[28] Estrogen upregulates PGE_2, which is a potent inducer of aromatase activity in endometriotic cells. Thus, there is a positive feedback loop within endometriotic implants. The aberrant expression of the aromatase in the endometriotic tissue may promote the survival and growth of endometriotic lesions.

Inhibition of aromatase activity in extraovarian sites with aromatase inhibitors may represent a new generation of medications for the treatment of endometriosis. Several potent and selective third-generation non-steroidal aromatase inhibitors are available, and, of these, anastrozole and

letrozole have substantial advantages over earlier agents in terms of efficacy and tolerability.[29] Although these agents have been widely used to treat postmenopausal patients with breast cancer, experience in the use of aromatase inhibitors in women with endometriosis is still limited (table II). Other agents, irreversible steroidal aromatase inactivators (such as exemestane), have been successfully used in breast cancer patients. However, the permanent inhibition of aromatase activity is contraindicated in women with endometriosis wishing to preserve their fertility and, therefore, the role of these drugs in selected women with endometriosis remains to be established.

4. Aromatase Inhibitors in the Treatment of Postmenopausal Endometriosis

The use of aromatase inhibitors in the treatment of postmenopausal endometriosis has been described only in case reports. Takayama et al.[30] described for the first time the use of aromatase inhibitors in the treatment of endometriosis. A patient who presented recurrent severe pain after hysterectomy, bilateral oophorectomy and resection of endometriosis received anastrozole for 9 months. This agent provided a quick improvement in pain symptoms and a decrease in the size of a 3 cm vaginal endometriotic nodule. The improvement in pain symptoms persisted 14 months after the cessation of treatment.[41] In another postmenopausal patient, the administration of letrozole resulted in an improvement in both pelvic pain and dyspareunia, which had previously persisted during other hormonal therapies (norethisterone and danazol).[31] Other case reports in postmenopausal women suggested that aromatase inhibitors might determine the regression not only of pain symptoms but also of endometriotic lesions. In a 55-year-old patient, the administration of letrozole resulted in the progressive regression of an 8×4 cm endometriotic lesion, which after 18 months of treatment measured 1 cm.[34] In another postmenopausal patient, the administration of letrozole improved the symptoms caused by an endometriotic nodule located in the posterior wall of the bladder. Notably, this patient was previously treated with another aromatase inhibitor, exemestane, for 2 weeks with no improvement in her symptoms.[39] In contrast with these reports, Bohrer et al.[40] reported that anastrozole was ineffective in preventing ureteral obstruction caused by endometriosis in a postmenopausal patient. This observation is not surprising; in fact, a deep endometriotic nodule may contain extensive fibrosis that does not respond to hormonal therapies (figure 1).

5. Aromatase Inhibitors in the Treatment of Premenopausal Endometriosis

Aromatase inhibitors can inhibit the production of extraovarian estrogens in adipose tissue, skin and endometriotic lesions. Aromatase inhibitors are usually administered to premenopausal women in combination with ovarian suppressive agents; this double-drug regimen may inhibit the production of both ovarian and extraovarian estrogens. Based on these considerations, some studies evaluated the efficacy of an aromatase inhibitor in improving pain symptoms related to the presence of endometriosis in premenopausal women.

The efficacy of aromatase inhibitors in premenopausal women was investigated for the first time in an open-label, nonrandomized study including ten patients.[32] Subjects of the study had pain symptoms that previously persisted despite both surgical and medical treatment; they underwent laparoscopy before and after the administration of letrozole. This agent caused a significant decrease in the intensity of pain symptoms and only one of ten patients did not have improvement in pain symptoms during treatment. In addition, second-look laparoscopies showed improvement in disease severity after treatment and histological examinations of peritoneal biopsies were negative for endometriosis. Unfortunately, this trial had several limitations. First, the study was not randomized. Second, the surgeon who performed all pre- and post-treatment laparoscopies was not blinded to the use of aromatase inhibitors and he was a scientific advisor for the pharmaceutical company that provided the funding for the study. In another study, Shippen and West[33]

Table II. Studies evaluating the effectiveness of aromatase inhibitors in the treatment of pain symptoms related to the presence of endometriosis

Study	Type of study	Hormonal state	Number of patients	Aromatase inhibitor	Additional treatment	Duration of treatment (mo)	Results	Follow-up (mo after completion of treatment)
Takayama et al.[30]	Case report	Postmenopausal	1	Anastrozole (oral, 1 mg/d)	Calcium (1.5 g/d), vitamin D (800 IU/d), alendronate (10 mg/d)	9	Regression of a vaginal endometriotic nodule, disappearance of pain symptoms	14
Razzi et al.[31]	Case report	Postmenopausal	1	Letrozole (oral, 2.5 mg/d)	Calcium (1 g/d), vitamin D (400 IU/d)	9	Improvement of pelvic pain and dyspareunia	0
Ailawadi et al.[32]	Open-label, nonrandomized, prospective	Premenopausal	10	Letrozole (oral, 2.5 mg/d)	Norethisterone (2.5 mg/d), calcium (1.25 g/d), vitamin D (800 IU/d)	6	Improvement in disease stage and ASRM score at laparoscopy, improvement in pain symptoms	1
Shippen and West[33]	Case report	Premenopausal	2	Anastrozole (oral, 1 mg/d)	Progesterone (oral, 200 mg/d), calcitriol (0.5 μg/d), rofecoxib (12.5 mg/d)	6	Reduction of symptoms, disappearance of endometriotic implants	24
Fatemi et al.[34]	Case report	Postmenopausal	1	Letrozole (oral, 2.5 mg/d)	Calcium (1.2 g/d), vitamin D (440 IU/d), sodium alendronate (70 mg/wk)	18	Regression of endometrioma, improvement in pain intensity	0
Amsterdam et al.[35]	Open-label, nonrandomized, prospective, multicentre	Premenopausal	18	Anastrozole (oral, 1 mg/d)	Ethinylestradiol (20 μg/d), levonorgestrel (0.1 mg/d)	6	Improvement in pain symptoms	0
Hefler et al.[36]	Open-label, nonrandomized, prospective	Premenopausal	10	Anastrozole (vaginal, 0.25 mg/d)	Calcium (1.25 g/d), vitamin D (800 IU/d)	6	Improvement in dysmenorrhoea, no change in chronic pelvic pain and dyspareunia	1
Remorgida et al.[37]	Open-label, nonrandomized, prospective	Premenopausal	12	Letrozole (oral, 2.5 mg/d)	Norethisterone (2.5 mg/d), calcium (1 g/d), vitamin D (880 IU/d)	6	Improvement in dysmenorrhoea, chronic pelvic pain and dyspareunia, and quick recurrence of pain symptoms after completion of treatment	6

Continued next page

Table II. Contd

Study	Type of study	Hormonal state	Number of patients	Aromatase inhibitor	Additional treatment	Duration of treatment (mo)	Results	Follow-up (mo after completion of treatment)
Remorgida et al.[38]	Open-label, nonrandomized, prospective	Premenopausal	12	Letrozole (oral, 2.5 mg/d)	Desogestrel (75 μg/d), calcium (1 g/d), vitamin D (880 IU/d)	6	Improvement in dysmenorrhoea and dyspareunia, quick recurrence of pain symptoms after completion of treatment	6
Mousa et al.[39]	Case report	Postmenopausal	1	Letrozole (oral, 2.5 mg three times per wk)	Micronized estradiol (0.5 mg/d during the last 4 mo of therapy)	8	Improvement in pain	0
Bohrer et al.[40]	Case report	Postmenopausal	1	Anastrozole (oral, 1 mg/d)		15	Improvement in pain symptoms, cessation of rectal bleeding, worsening renal function requiring surgery	0

ASRM = American Society for Reproductive Medicine.

investigated the effectiveness of anastrozole combined with oral progesterone and rofecoxib in two premenopausal women who had pain symptoms resistant to previous surgical and hormonal therapies. Both patients had improvement in pain symptoms during the 6-month treatment with the aromatase inhibitor. One of the patients had a persistent improvement in pain symptoms for over 24 months after treatment. The other patient underwent laparoscopy 15 months after cessation of therapy because of abdominal and pelvic pain; however, there was no evidence of endometriosis at surgery and only minimal adhesions were present. These preliminary findings were subsequently confirmed in another prospective open-label trial.[35] Eighteen premenopausal women with pain symptoms resistant to previous surgical and hormonal treatments were included in the study. They received anastrozole and an oral contraceptive pill for 6 months. Three patients discontinued the study; one of them had no pain relief during treatment. Fourteen of the 15 patients who completed the 6-month treatment had significant improvement in pain symptoms with minimal adverse effects. Unfortunately, no follow-up of pain symptoms after discontinuation of treatment was reported. Another pilot study examined the effects of vaginally administered anastrozole (0.25 mg of anastrozole in a 2 g vaginal suppository with Adeps neutralis as suppository base) in ten premenopausal women with rectovaginal endometriosis.[36] An improvement in dysmenorrhoea, physical and social functioning was observed; however, chronic pelvic pain and dyspareunia did not improve during therapy.

Two recent studies confirmed the efficacy of aromatase inhibitors in reducing the intensity of pain symptoms related to the presence of endometriosis and reported the follow-up after discontinuation of treatment.[37,38] An open-label prospective study including 12 women of reproductive age evaluated the efficacy of letrozole combined with norethisterone acetate in the treatment of pain symptoms related to the presence of rectovaginal endometriosis.[37] The intensity of deep dyspareunia and chronic pelvic pain decreased significantly during treatment; however, pain symptoms recurred 3 months after

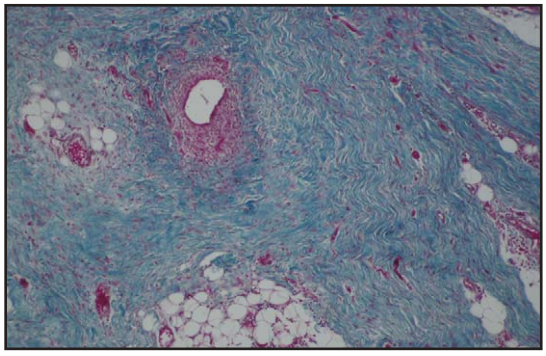

Fig. 1. Section of a rectovaginal endometriotic nodule stained with masson trichrome technique (blue staining indicates the fibrosis, red staining indicates the muscle).

the completion of treatment. At 6-month follow-up, no significant difference was observed in the intensity of dysmenorrhoea, dyspareunia and chronic pelvic pain when compared with baseline values. Interestingly, some of the patients included in the study underwent surgical excision of endometriotic lesions; the histological examination of these specimens demonstrated the preservation of endometrial glands and a high proliferative activity in the stroma (figure 2). In another study performed by the same authors,[38] letrozole was combined with the desogestrel-only contraceptive pill. This double-drug regimen caused the formation of functional ovarian cysts in all the patients, which required the interruption of treatment. However, the therapy determined a quick improvement in the intensity of dysmenorrhoea and dyspareunia. Unfortunately, pain symptoms immediately recurred when treatment was stopped.

6. Aromatase Inhibitors in the Prevention of Recurrence after Surgical Excision of Endometriosis

Only one study has investigated the effectiveness of aromatase inhibitors in preventing the recurrence of endometriosis in premenopausal women after conservative surgery. In a prospective, randomized, placebo-controlled trial, 80 women who underwent conservative surgery for severe endometriosis were assigned to receive either anastrozole (1 mg/day) plus subcutaneous depot injections of goserelin 3.6 mg (every 4 weeks for 24 weeks) or a placebo tablet in addition to this goserelin regimen for 24 weeks.[42] The double-drug regimen increased the pain-free interval and decreased symptom recurrence rates when compared with goserelin alone. In fact, during the follow-up period of 24 months after the post-surgical medical treatment, three patients of 40 experienced recurrence in the goserelin plus anastrozole arm (7.5%), whereas recurrences were detected in 14 patients of 40 in the goserelin-only arm (35%).

7. Adverse Effects Determined with Aromatase Inhibitors in Women with Endometriosis

No published study reported severe adverse effects associated with the administration of aromatase inhibitors in premenopausal women with endometriosis. Some patients experienced hot flashes/flushes, mood swings, headache, vaginal spotting, fatigue, dizziness, depression, weight gain, increase appetite, heavy vaginal bleeding, muscle aches, bone and joint pain, insomnia, rash and decreased libido.[32,35,37,38] Several studies investigated the effects of aromatase inhibitors on bone mineral density demonstrating that the short-term administration of aromatase inhibitors does not determine significant reduction on spine and hip-bone densities in either premenopausal[32,34,35-38] or postmenopausal patients.[30,31]

8. Conclusions

Over the last 10 years, the use of aromatase inhibitors in the treatment of pain symptoms caused by endometriosis has been subject of several reports and of much debate in scientific meetings. However, until now, only a few clinical studies have assessed the efficacy of these agents in reducing pain symptoms in women with endometriosis and, more importantly, these investigations had several limitations. Most of the available data are based on case reports or observational studies, and no randomized, placebo-controlled trial has been

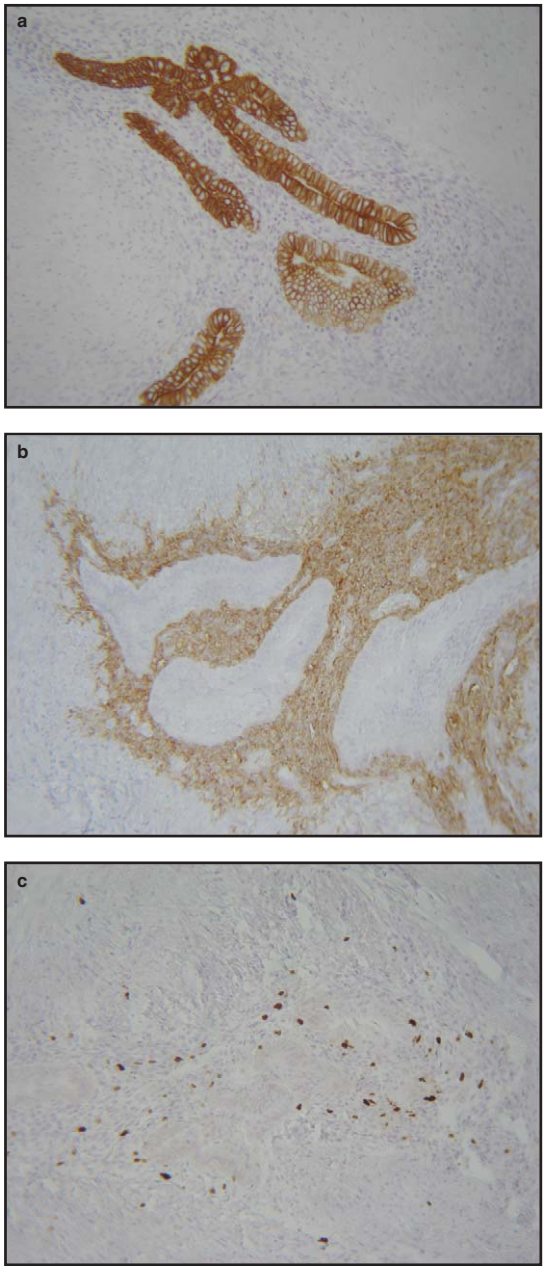

Fig. 2. Serial sections of a rectovaginal endometriotic nodule removed 3 months after the completion of a 6-month treatment with letrozole and norethisterone acetate. (**a**) CK7 staining confirms the preservation of the glandular epithelium; (**b**) CD10 staining shows the abundance of stromal cells; (**c**) Ki67 staining demonstrates the proliferative activity in the stromal cells.

performed on this topic. In fact, the only randomized, placebo-controlled trial evaluated the efficacy of aromatase inhibitors in preventing the recurrence of pain after surgery.[42] In addition, no published trial compared the efficacy of the combination of aromatase inhibitors with another hormonal therapy (such as GnRH analogues, oral contraceptive pill or progestins) with the efficacy of the administration of the hormonal therapy alone. Another relevant limitation of the available literature is that, excluding case reports, only two studies reported a short-term follow-up (6 months) after interruption of treatment with aromatase inhibitors.[37,38] The two studies were published by the same group of investigators and showed a quick recurrence of pain symptoms after the interruption of aromatase inhibitor administration. Finally, a range of results has been reported on the effects of aromatase inhibitors on endometriotic lesions. Some case reports described the reduction in the size of endometriotic lesions after long-term administration of aromatase inhibitors.[30,34] One observational study demonstrated that at second-look laparoscopies, the American Society for Reproductive Medicine score was decreased in all the patients treated with letrozole and norethisterone (northindrone) for 6 months. In addition, although endometriosis was laparoscopically recognizable in eight of ten women with endometriosis, biopsies of these lesions were negative for endometriosis.[32] In contrast with the findings of these studies, one case report[40] and one observational study[37] confirmed the presence of deep endometriosis after the use of aromatase inhibitors.

Several questions on the use of aromatase inhibitors in endometriosis are unanswered. The long-term course of pain symptoms after the interruption of aromatase administration remains to be evaluated. The superiority of these expensive agents in improving pain symptoms with respect to cheaper hormonal therapies (such as progestins) remains to be proved. Finally, although the studies included in this article suggest that aromatase inhibitors are well tolerated even in women of reproductive age, definitive data are not available. In particular, the potential effects of aromatase inhibitors on the bone

should be considered in patients using aromatase inhibitors for longer than 6 months.

On the basis of the available data, administration of aromatase inhibitors should now be offered only to the small number of women who have severe pain despite previous surgical and hormonal therapies. Aromatase inhibitors may be useful in reducing pain associated with endometriosis; however, further research in the form of well powered, randomized, controlled trials will be required before recommending the routine use of these agents.[43]

Acknowledgements

The authors thank Prof. Ezio Flucheri for providing the histological images used in the study. No sources of funding were used to assist in the preparation of this review. The authors have no conflicts of interest that are directly relevant to the content of this review.

References

1. Kennedy S, Bergqvist A, Chapron C, et al. ESHRE guideline for the diagnosis and treatment of endometriosis. Hum Reprod 2005 Oct; 20 (10): 2698-704
2. Guo SW, Wang Y. Sources of heterogeneities in estimating the prevalence of endometriosis in infertile and previously fertile women. Fertil Steril 2006 Dec; 86 (6): 1584-95
3. Guo SW, Wang Y. The prevalence of endometriosis in women with chronic pelvic pain. Gynecol Obstet Invest 2006; 62 (3): 121-30
4. Sampson JA. Peritoneal endometriosis due to menstrual dissemination of endometrial tissue into the peritoneal cavity. Am J Obst Gynecol 1927; 14: 442-69
5. Halme J, Hammond MG, Hulka JF, et al. Retrograde menstruation in healthy women and in patients with endometriosis. Obstet Gynecol 1984 Aug; 64 (2): 151-4
6. Gazvani R, Templeton A. Peritoneal environment, cytokines and angiogenesis in the pathophysiology of endometriosis. Reproduction 2002 Feb; 123 (2): 217-26
7. Capellino S, Montagna P, Villaggio B, et al. Role of estrogens in inflammatory response: expression of estrogen receptors in peritoneal fluid macrophages from endometriosis. Ann N Y Acad Sci 2006 Jun; 1069: 263-7
8. Montagna P, Capellino S, Villaggio B, et al. Peritoneal fluid macrophages in endometriosis: correlation between the expression of estrogen receptors and inflammation. Fertil Steril 2008 Jul; 90 (1): 156-64
9. Hornstein MD, Hemmings R, Yuzpe AA, et al. Use of nafarelin versus placebo after reductive laparoscopic surgery for endometriosis. Fertil Steril 1997 Nov; 68 (5): 860-4
10. Busacca M, Chiaffarino F, Candiani M, et al. Determinants of long-term clinically detected recurrence rates of deep, ovarian, and pelvic endometriosis. Am J Obstet Gynecol 2006 Aug; 195 (2): 426-32
11. Shakiba K, Bena JF, McGill KM, et al. Surgical treatment of endometriosis: a 7-year follow-up on the requirement for further surgery. Obstet Gynecol 2008 Jun; 111 (6): 1285-92
12. Muzii L, Marana R, Caruana P, et al. Postoperative administration of monophasic combined oral contraceptives after laparoscopic treatment of ovarian endometriomas: a prospective, randomized trial. Am J Obstet Gynecol 2000 Sep; 183 (3): 588-92
13. Vercellini P, Somigliana E, Daguati R, et al. Postoperative oral contraceptive exposure and risk of endometrioma recurrence. Am J Obstet Gynecol 2008 May; 198 (5): 504 e1-5
14. Allen C, Hopewell S, Prentice A. Non-steroidal antiinflammatory drugs for pain in women with endometriosis. Cochrane Database Syst Rev 2005; (4): CD004753
15. Luciano AA, Turksoy RN, Carleo J. Evaluation of oral medroxyprogesterone acetate in the treatment of endometriosis. Obstet Gynecol 1988 Sep; 72 (3 Pt 1): 323-7
16. Vercellini P, De Giorgi O, Oldani S, et al. Depot medroxyprogesterone acetate versus an oral contraceptive combined with very-low-dose danazol for long-term treatment of pelvic pain associated with endometriosis. Am J Obstet Gynecol 1996 Aug; 175 (2): 396-401
17. Crosignani PG, Luciano A, Ray A, et al. Subcutaneous depot medroxyprogesterone acetate versus leuprolide acetate in the treatment of endometriosis-associated pain. Hum Reprod 2006 Jan; 21 (1): 248-56
18. Fedele L, Bianchi S, Zanconato G, et al. Use of a levonorgestrel-releasing intrauterine device in the treatment of rectovaginal endometriosis. Fertil Steril 2001 Mar; 75 (3): 485-8
19. Petta CA, Ferriani RA, Abrao MS, et al. Randomized clinical trial of a levonorgestrel-releasing intrauterine system and a depot GnRH analogue for the treatment of chronic pelvic pain in women with endometriosis. Hum Reprod 2005 Jul; 20 (7): 1993-8
20. Dlugi AM, Miller JD, Knittle J. Lupron depot (leuprolide acetate for depot suspension) in the treatment of endometriosis: a randomized, placebo-controlled, double-blind study. Lupron Study Group. Fertil Steril 1990 Sep; 54 (3): 419-27
21. Bergqvist A, Bergh T, Hogstrom L, et al. Effects of triptorelin versus placebo on the symptoms of endometriosis. Fertil Steril 1998 Apr; 69 (4): 702-8
22. Ferrero S, Abbamonte LH, Anserini P, et al. Future perspectives in the medical treatment of endometriosis. Obstet Gynecol Surv 2005 Dec; 60 (12): 817-26
23. Ferrero S, Ragni N, Remorgida V. Antiangiogenic therapies in endometriosis. Br J Pharmacol 2006 Sep; 149 (2): 133-5
24. Baxendale PM, Reed MJ, James VH. Inability of human endometrium or myometrium to aromatize androstenedione. J Steroid Biochem 1981 Mar; 14 (3): 305-6
25. Bulun SE, Mahendroo MS, Simpson ER. Polymerase chain reaction amplification fails to detect aromatase cytochrome P450 transcripts in normal human endometrium or decidua. J Clin Endocrinol Metab 1993 Jun; 76 (6): 1458-63
26. Noble LS, Simpson ER, Johns A, et al. Aromatase expression in endometriosis. J Clin Endocrinol Metab 1996 Jan; 81 (1): 174-9
27. Kitawaki J, Noguchi T, Amatsu T, et al. Expression of aromatase cytochrome P450 protein and messenger

ribonucleic acid in human endometriotic and adenomyotic tissues but not in normal endometrium. Biol Reprod 1997 Sep; 57 (3): 514-9

28. Noble LS, Takayama K, Zeitoun KM, et al. Prostaglandin E2 stimulates aromatase expression in endometriosis-derived stromal cells. J Clin Endocrinol Metab 1997 Feb; 82 (2): 600-6
29. Santen RJ, Harvey HA. Use of aromatase inhibitors in breast carcinoma. Endocr Relat Cancer 1999 Mar; 6 (1): 75-92
30. Takayama K, Zeitoun K, Gunby RT, et al. Treatment of severe postmenopausal endometriosis with an aromatase inhibitor. Fertil Steril 1998 Apr; 69 (4): 709-13
31. Razzi S, Fava A, Sartini A, et al. Treatment of severe recurrent endometriosis with an aromatase inhibitor in a young ovariectomised woman. BJOG 2004 Feb; 111 (2): 182-4
32. Ailawadi RK, Jobanputra S, Kataria M, et al. Treatment of endometriosis and chronic pelvic pain with letrozole and norethindrone acetate: a pilot study. Fertil Steril 2004 Feb; 81 (2): 290-6
33. Shippen ER, West Jr WJ. Successful treatment of severe endometriosis in two premenopausal women with an aromatase inhibitor. Fertil Steril 2004 May; 81 (5): 1395-8
34. Fatemi HM, Al-Turki HA, Papanikolaou EG, et al. Successful treatment of an aggressive recurrent postmenopausal endometriosis with an aromatase inhibitor. Reprod Biomed Online 2005 Oct; 11 (4): 455-7
35. Amsterdam LL, Gentry W, Jobanputra S, et al. Anastrazole and oral contraceptives: a novel treatment for endometriosis. Fertil Steril 2005 Aug; 84 (2): 300-4
36. Hefler LA, Grimm C, van Trotsenburg M, et al. Role of the vaginally administered aromatase inhibitor anastrozole in women with rectovaginal endometriosis: a pilot study. Fertil Steril 2005 Oct; 84 (4): 1033-6
37. Remorgida V, Abbamonte HL, Ragni N, et al. Letrozole and norethisterone acetate in rectovaginal endometriosis. Fertil Steril 2007 Sep; 88 (3): 724-6
38. Remorgida V, Abbamonte LH, Ragni N, et al. Letrozole and desogestrel-only contraceptive pill for the treatment of stage IV endometriosis. Aust N Z J Obstet Gynaecol 2007 Jun; 47 (3): 222-5
39. Mousa NA, Bedaiwy MA, Casper RF. Aromatase inhibitors in the treatment of severe endometriosis. Obstet Gynecol 2007 Jun; 109 (6): 1421-3
40. Bohrer J, Chen CC, Falcone T. Persistent bilateral ureteral obstruction secondary to endometriosis despite treatment with an aromatase inhibitor. Fertil Steril 2008 Nov; 90 (5): 2004 e7-9
41. Takayama K, Zeitoun K, Carr BR, et al. Medical versus surgical treatment of endometriosis? Reply to authors. Fertil Steril 1998; 70 (6): 1183-4
42. Soysal S, Soysal ME, Ozer S, et al. The effects of post-surgical administration of goserelin plus anastrozole compared to goserelin alone in patients with severe endometriosis: a prospective randomized trial. Hum Reprod 2004 Jan; 19 (1): 160-7
43. Nawathe A, Patwardhan S, Yates D, et al. Systematic review of the effects of aromatase inhibitors on pain associated with endometriosis. BJOG 2008 Jun; 115 (7): 818-22

Correspondence: Dr *Simone Ferrero*, Department of Obstetrics and Gynecology, San Martino Hospital and University of Genoa, Largo R. Benzi 1, 16132 Genoa, Italy.
E-mail: dr@simoneferrero.com