Mohamed FM Mitwally, Robert F Casper

Chapter 29

Aromatase Inhibitors for Endometriosis

Introduction

This chapter discusses the theory and available evidence for the use of the group of medications called "aromatase inhibitors" in managing health problems associated with endometriosis. The chapter is meant for clinicians dealing with women suffering from endometriosis. For that reason, emphasis will be placed on clinical aspects rather than theories and hypotheses with focus on practical guidelines for the use of aromatase inhibitors in the management of endometriosis.

The aromatase enzyme catalyzes a terminal steroidogenesis step that leads to estrogen synthesis, by converting androgens into estrogens in a unidirectional pathway. The third-generation aromatase inhibitors include medications that halt estrogen synthesis by specifically inhibiting the aromatase enzyme. Aromatase inhibitors have been approved for women with *"postmenopausal"* breast cancer, an estrogen-dependant cancer that would benefit from suppression of estrogen synthesis. Endometriosis is an estrogen-dependant disease often encountered in *"premenopausal"* women who frequently suffer from pain and associated infertility.

The pioneering work of Bulun[1-3] and other investigators[4] confirmed the expression of aromatase in endometriotic tissues and highlighted the significant role played by local estrogen synthesis in the progress of endometriosis. We had previously reported the effectiveness of one of the third generation aromatase inhibitors in suppressing estrogen levels in *"premenopausal"* women[5-12] suggesting that aromatase inhibitors might also be a successful tool in the management of estrogen-dependant disorders such as endometriosis, outside the traditional postmenopausal indication.

This chapter has two parts: first part discusses the underlying theory behind the potential role for aromatase inhibitors in managing endometriosis, while the second part discusses the available evidence in the literature for the success of such clinical application. From a clinical perspective, pain and infertility, the two predominant health issues associated with endometriosis will be the key points for discussion.

We will try to answer the following questions;

- Is there a sound scientific hypothesis to support the use of aromatase inhibitors in managing endometriosis?
- What is the existing clinical evidence that supports this novel application?
- Is there a difference among various aromatase inhibitors for such application?
- What is the optimal regimen for managing endometriosis with aromatase inhibitors?

Scientific Hypothesis Behind using Aromatase Inhibitors for Endometriosis

Estrogen Synthesis and Production

Estrogens are C-18 steroids (contain 18 carbon atoms), characterized by the presence of an *"aromatic"* ring, with estradiol, the strongest estrogen, containing a *"hydroxyl"* group at C17 while, estrone, a much weaker estrogen, has a *"ketone"* group at the C17 position.[13, 14] In premenopausal women, the ovaries are the principle source of estrogen production, mainly estradiol, which functions as a circulating hormone to act on distal target tissues. On the other hand, in postmenopausal women when the ovaries cease to produce estrogen, estrogen is produced in a number of extragonadal sites from the circulating C-19 steroids (androgens), a step catalyzed by the aromatase enzyme. Estrogen produced in extragonadal tissues acts locally at these sites as a paracrine or even intracrine factor. These sites include the mesenchymal cells of adipose

tissue, breast, osteoblasts and chondrocytes of bone, the vascular endothelium and aortic smooth muscle cells, and numerous sites in the brain. Thus, circulating levels of estrogens in postmenopausal women are not the drivers of estrogen action; they are a spillover from local tissue production. Therefore, circulating levels reflect rather than regulate estrogen action in postmenopausal women.

Interestingly, the control of local estrogen production is modulated through the changes of aromatase. There are distinct tissue-specific promotors of aromatase, each of which is regulated by different hormonal factors and second messenger signaling pathways.[15] Estrogen production is most commonly thought of as an endocrine product of the gonads. However, as mentioned above, there are many tissues that express the aromatase enzyme, and thus have the capacity to synthesize estrogens from circulating androgens. A non-gonadal source of estrogen, in addition to its local action, can sometimes contribute significantly to the circulating pool of estrogens e.g. adipose tissue estrogen contribution. There is increasing evidence that in both men and women extra-glandular production of estrogens from androgens is important in normal physiology, as well as in pathophysiologic states.[16]

Aromatase expression in adipose tissue, and possibly in the skin primarily accounts for the extraglandular (peripheral) formation of estrogen and increases as a function of ***body weight*** and ***advancing age***. Sufficient circulating levels of the biologically active estrogen, estradiol, can be produced as a result of extra glandular aromatization of androstenedione to estrone that is subsequently reduced to estradiol in peripheral tissues. Such biologically active estradiol can activate several estrogen-dependant reproductive disorders including endometriosis, abnormal uterine bleeding, endometrial hyperplasia and cancer.[16, 17]

Aromatase Inhibitors

Blocking estrogen production by inhibiting the enzyme catalyzing the main step of its synthesis from androgens (aromatase enzyme) is an exciting treatment modality for estrogen-dependant disorders. Such treatment has been in clinical application for more than half a century since the development of the first generation of aromatase inhibitors such as aminoglutethimide. However, the clinical applications of the aromatase inhibitors in managing estrogen-dependant disorders had not achieved significant success until recently. This was due to several problems encountered with the clinical use of early generations of the aromatase inhibitors. Those problems were successfully overcome to a great extent by the development of the third generation of aromatase inhibitors. **Table 29-1** summarizes the different generations of the aromatase inhibitors. Box 1 summarizes the main problems associated with the early-generations of the aromatase inhibitors, while box 2 summarizes the advantages of the third generation aromatase inhibitors.

Development of Aromatase Inhibitors

The location of the estrogen synthesis catalyzed by aromatase at the far end of steroidogenesis cascade makes this terminal step a good target for selective inhibition without significant effect on substrate accumulation. Several aromatase inhibitors have been developed over the last five decades with the third generation aromatase inhibitors licensed in the last decade for suppressing

Table 29-1: Different generations of aromatase inhibitors

Generation	*Non-Steroidal Aromatase Inhibitors*	*Steroidal Aromatase Inhibitors (Sometimes called suicidal inhibitors of the aromatase enzyme)*
	Work by temporary (reversible) inactivation of the aromatase enzyme	Work by permanent (irreversible) inactivation of the aromatase enzyme.
First Generation	Aminoglutethimide (Cytadren®)	N/A
Second Generation	Rogletimide Fadrozole	Formestane
Third Generation	Letrozole (Femara® 2.5 mg/tablet) Anastrozole (Arimidex® 1mg/tablet) Vorozole	Exemestane (Aromasin® 25 mg/tablet)

estrogen synthesis in postmenopausal women with breast cancer. The third generation aromatase inhibitors were developed after the clinical failure of the earlier generations of aromatase inhibitors as explained above in **Boxes 29-1 and 29-2.**

Third-generation aromatase inhibitors

The third-generation aromatase inhibitors effectively block estrogen synthesis without exerting effects on other steroidogenic pathways and have been heralded as a "triumph of translational oncology". This group includes the non-steroidal letrozole (Femara®) and anastrozole (Arimidex®), and the steroidal exemestane (Aromasin®). These aromatase inhibitors are currently available for clinical use as oral tablets. They have been approved for estrogen suppression in postmenopausal women with breast cancer.[18]

Structure: Third generation non-steroidal aromatase inhibitors are nitrogen-containing triazole derivatives that bind to iron in the heme moiety of the aromatase enzyme resulting in reversible inhibition.[19]

Box 1: Problems associated with early generations aromatase inhibitors

Pharmacodynamic advantages:
1. Low potency in inhibiting the aromatase enzyme particularly in premenopausal women (very low potency)
2. Lack of specificity in inhibiting the aromatase enzyme with significant inhibition of other steroidogenesis enzymes leading to medical adrenalectomy.

Pharmacokinetic advantages:
1. Not all members are available orally (some require parentral administration
2. Variable bioavailability after oral administration
3. Variable half life that is changes with the period of administration due to induction of its metabolism

Clinical Advantages:
1. Poorly tolerated on daily administration with more a third of patients discontinued treatment due to adverse effects
2. Significant side effects related to both the aromatase inhibitors e.g. drowsiness, morbilliform skin rash, nausea and anorexia, and dizziness and side effects secondary to the steroids used for replacement therapy e.g. glucocorticoids
3. Interaction with alcohol with significant potentiation of its action
4. Significant interactions with other medications e.g. coumarin and warfarin.
5. Need for replacement therapy due to medical adrenalectomy e.g. glucocorticoid and mineralocorticoid replacement
6. Long-term possible carcinogenesis (at least in animals)

Box 2: Advantages of third-generation aromatase inhibitors

Pharmacodynamic advantages:
1. Extreme potency in inhibiting the aromatase enzyme (up to thousand times potency of the first generation aminoglutethimide)
2. Very specific in inhibiting the aromatase enzyme without significant inhibition of the other steroidogenesis enzymes. This is true even at high doses
3. Absence of estrogen receptor depletion

Pharmacokinetic advantages:
1. Orally administered (other routes of administration are also possible e.g. vaginal and rectal)
2. Almost 100% bioavailability after oral administration
3. Rapid clearance from the body due to short half-life, (~ 8 hours for the Aromasin® to ~ 45 hours for the Femara® and Arimidex®)
4. Absence of tissue accumulation of the medications or any of their metabolites
5. No significant active metabolites

Clinical Advantages:
1. Well tolerated on daily administration for up to several years (in post-menopausal women with breast cancer) with few adverse effects
2. Few mild side effects
3. Very safe without significant contraindications
4. Absence of significant interactions with other medications
5. Very wide safety margin (toxic dose is several thousand times higher than recommended efficacious therapeutic dose)
6. Relatively inexpensive

Potency: Aromatase inhibition and estradiol suppression show good correlation and are consistently significantly higher (more than a thousand times) for third-generation aromatase inhibitors when compared with first-generation and second-generation aromatase inhibitors.[20] In cell-free aromatase system experiments (human placental microsomes), letrozole has been found equipotent to anastrozole in inhibiting the aromatase enzyme. However, letrozole was found to be 10–30 times more potent than anastrozole in inhibiting intracellular aromatase in "intact" rodent cells, human adipose fibroblasts, and human cancer cell lines.[21] Compared to other aromatase inhibitors, letrozole has consistently demonstrated greater potency.[22, 23]

Selectivity: Third generation aromatase inhibitors are highly selective for the aromatase enzyme and unlike first- and second-generation aromatase inhibitors do not affect glucocorticoids, mineralocorticoiods, or thyroxine secretion. In vivo adrenocorticotrophic hormone (ACTH) stimulation tests in rats showed that letrozole had no

significant effect on either aldosterone or corticosterone levels, even at a dose 1,000 times greater than that required for inhibition of aromatase.[24] The vast majority of patients treated with letrozole have a normal response to synthetic ACTH.[25]

Pharmacokinetics: Third generation aromatase inhibitors enjoy several pharmacokinetic advantages that make them convenient for clinical practice. This includes almost 100% absorption following oral administration with large apparent volume of distribution due to extensive distribution to various body tissues. The terminal half-life is usually around two days with steady-state concentrations reached usually in less than one week of daily administration. Such steady state is maintained for long periods with no evidence of drug accumulation.[26]

Another major pharmacokinetic advantage that third generation aromatase inhibitors have over the first-generation aromatase inhibitor aminoglutethimide, is the absence of significant drug interactions except when combined with tamoxifen as the case with letrozole. Its plasma concentration is reduced by between 35% and 40% when combined with tamoxifen.[27] However, hepatic impairment can markedly increase the terminal half-life.[26]

Is there a Difference in Response to Individual Aromatase Inhibitors?

This is an important question that is difficult to answer, because the third generation aromatase inhibitors suppress estrogen synthesis strongly enough to bring down estrogen levels below the detection limits of the currently available hormonal assays.[28] However, in a cross-over study between anastrozole and letrozole, the latter was found to be the more potent inhibitor of total body aromatization, and plasma estrogen.[29] In a recent study, the same group recorded a more potent suppression of tissue estrogens with letrozole compared to previous results with anastrozole, without significant inter-individual variability.[30] However, whether such difference in estrogen suppression potency is translated into clinical differences, is still a matter of controversy and awaits future studies.

Non-aromatase Inhibition Actions of Third Generation Aromatase Inhibitors

The presence of other mechanisms of action for the aromatase inhibitors that are not dependant on inhibiting the aromatase enzyme and suppressing estrogen synthesis have been suggested. One such suggestion comes from a three-dimensional fibrin matrix model for in-vitro study of endometrial explant growth. In this model, letrozole was found to have a growth stimulatory effect on normal human endometrium rather than a suppression of proliferation and angiogenesis as would be expected from aromatase inhibition and estrogen suppression.[31] The authors suggested a possible mechanism though an effect on insulin-like growth factor 1 (IGF-1), known to be synthesized locally in endometrium. All three IGF-1 isoforms are expressed in eutopic endometrium and in endometriomas.[32] Also, the human endometrium is known to have high-affinity receptors for IGF-1,[33] and proliferative activity of uterine cells may be regulated by IGF-1.[34] These speculations of a direct endometrial effect of letrozole or other members of the third generation aromatase inhibitors are still unconfirmed and await further studies.

Differences among Aromatase Inhibitors

Potency of different third generation aromatase inhibitors

There is usually a correlation between the in-vitro and in-vivo efficacy of the aromatase inhibitors. However, *in vivo* measurements of the efficacy of an aromatase inhibitor depends on other important factors including drug metabolism e.g. terminal half-life and tissue distribution. This may result in a significant difference between what is seen in *in vitro* experiments and in vivo effects.[35] A clear example is the second-generation aromatase inhibitors, which *in vitro* revealed a higher biochemical efficacy when compared with the third-generation inhibitors, but *in vivo* showed a significantly lower suppression of plasma estrogens that translated into an inferior clinical efficacy.[36]

Letrozole was found to have greater potency (both in vivo and in vitro) than all the other aromatase inhibitors, including anastrozole, exemestane, formestane, and aminoglutethimide. Moreover, letrozole produced near complete inhibition of aromatase in peripheral tissues and was associated with greater suppression of estrogen than other aromatase inhibitors.[37]

Adverse Effects Associated with Third Generation Aromatase Inhibitors

Almost all available data on the side effects and adverse reactions associated with third generation aromatase inhibitors come from clinical trials involving postmenopausal women with advanced breast cancer. In general, third generation aromatase inhibitors have been found very well tolerated with few significant side affects and a low rate of discontinuation due to adverse reactions. If this is the case in such a vulnerable elderly population (post-menopausal women with advanced breast cancer), the use of third generation aromatase inhibitors in

premenopausal women during the reproductive age, would be expected to be very well tolerated.

When considering side effects and adverse reactions associated with third generation aromatase inhibitors we should consider two groups of problems:

First: problems related to the medications themselves rather than their estrogen action. There are no known serious side effects reported with third generation aromatase inhibitors other than mild non-specific ones such as headaches and gastrointestinal symptoms. Arthralgia is an interesting problem that has been seen more frequently with third generation aromatase inhibitors treatment and will be discussed later. Second: problems related to estrogen deprivation due to suppression of estrogen synthesis. Those include menopausal symptoms such as hot flashes and vaginal dryness, as well as long-term effects of estrogen deprivation especially on the bones and lipid profile.[38]

The following is a brief discussion of some significant adverse effects associated with aromatase inhibitors use. It is important to reiterate here that most of those adverse effects were associated with long term use of third generation aromatase inhibitors administered daily for several years in postmenopausal women with breast cancer.

Arthralgia: An important unique side effect that has been found associated with third generation aromatase inhibitors is joint pain (arthralgia) that appears to be quite prevalent and seen more commonly than with tamoxifen use. In some cases, arthralgia was severe enough to be a reason for discontinuation of aromatase inhibitor treatment. The possible mechanisms of aromatase inhibitor-associated arthralgia are still unclear. Treatment options for arthralgia including non-steroidal anti-inflammatory drugs are currently inadequate. High-dose vitamin D and new-targeted therapies to inhibit bone loss are being investigated.[39]

Effect on bone: Third generation aromatase inhibitors were found to increase bone turnover and induce bone loss particularly at sites rich in trabecular bone. In these sites, bone loss averaged 1–3% per year leading to an increase in fracture incidence compared to that seen during tamoxifen use. Such adverse bone effect was found more in younger women with rates of bone loss averaging 7–8% per year of daily use. To reduce the severity of bone loss, osteoporosis, and the risk of fracture, randomized clinical trials in postmenopausal women found bisphosphonates to significantly reduce bone loss caused by aromatase inhibitor therapy. This treatment along with a healthy lifestyle and adequate intake of calcium and vitamin D are currently the treatments of choice to prevent bone loss.[40] However, for younger women in the reproductive age, the use of bisphosphonates should be avoided in those still desiring fertility. Add back estrogen is a more appealing option to prevent bone loss associated with long-term use of aromatase inhibitors in young women.

Effects on blood lipids: There are concerns about increasing cardiovascular risks from estrogen deprivation caused by aromatase inhibitors, through adverse effect on blood lipids. Concerns about negative lipid changes associated with aromatase inhibitors that could increase cardiovascular adverse events are still unclear. The available data on effects of third generation aromatase inhibitors on serum lipids are limited to short-term studies that found different effects exerted by different aromatase inhibitors. Exemestane was suggested to have little or possibly a slight beneficial effect on serum lipids. This could be due to its steroid nature, while anastrozole appeared to have possibly a little adverse effect; letrozole was suggested to have a detrimental effect. However, the data are limited and long-term studies are still needed.[40]

Aromatase Enzyme in Endometriotic Tissues

Significant levels of aromatase enzyme activity and expression have been detected in the stromal cell component of endometriosis.[1] In addition, the eutopic endometrium of women with endometriosis has been found to contain low but significant levels of aromatase enzyme activity and expression. The authors suggested that upon retrograde menstruation followed by implantation of this inherently abnormal tissue (cells from eutopic endometrium) on the peritoneal surfaces, expression and activity of the aromatase enzyme are amplified.[1,2]

There are tissue-specific promotors that enhance the expression of the aromatase enzyme. Extraovarian endometriotic tissue and ovarian endometrioma cells almost exclusively use promoter II, which is the proximal promoter responsive to prostaglandin E2 (PGE2) and cyclic adenosine monophosphate (cAMP), for aromatase expression in vivo.[2,3] Other molecular abnormalities have been demonstrated including the presence of significant levels of StAR in addition to aromatase activity both in ectopic and eutopic endometrium of patients with endometriosis. Prostaglandin E2 is a potent inducer of both StAR and aromatase in endometriotic stromal cells. In addition, a transcription factor, steroidogenic factor 1, is also aberrantly expressed and binds to steroidogenic promoters in endometriotic tissues. Steroidogenic

factor 1 mediates PGE2–cAMP dependent co-activation of multiple steroidogenic genes, most notably StAR and aromatase.[3]

The enzyme cyclooxygenase-2 (COX-2) that catalyzes the conversion of arachidonic acid to PGE2 is significantly up-regulated in stromal cells of both endometriotic tissue and endometrium of women with endometriosis.[41, 42] Estradiol is a potent stimulator of COX-2 in uterine endothelial cells, which may create a vicious circle of positive feedback involving StAR and aromatase expression. Increased synthesis of E2 stimulates COX-2 leading to PGE2 synthesis that in turn promotes the expression and activity of both StAR and aromatase, thereby leading to the further formation of estrogen.

Aromatase Inhibitors in Premenopausal Women

As indicated earlier, endometriosis is most often encountered in reproductive age women. Use of aromatase inhibitors to suppress estrogen production in reproductive age women has two significant problems due to the presence of functioning ovaries:

First: aromatase expression and potency in functioning ovaries (mainly the granulosa cells) is known to be much greater compared to postmenopausal women.

Second: In response to estrogen deprivation by aromatase inhibition, endogenous gonadotropins rise and lead to stimulation of de novo aromatase synthesis in the ovaries. This will lead to escape from the aromatase inhibitor effect on estrogen synthesis. In addition, follicular cysts may develop.

In contrast to the brain, endometriotic tissue, or adipose tissue, there are overwhelming levels of aromatase expression in the ovaries of premenopausal women (granulosa cells of the growing follicles particularly the Graafian follicle). Thus, it is expected that aromatase inhibitors in premenopausal women would inhibit aromatase activity in peripheral tissues such as the brain, endometriosis, and adipose tissues totally. On the other hand, only partial aromatase activity blockade may be expected in the ovary.[43] Therefore, higher doses of aromatase inhibitors are required in premenopausal women than those successfully applied in postmenopausal women to achieve comparable total body aromatase inhibition.

As mentioned earlier, the compensatory rise in endogenous gonadotropins, particularly FSH leads to de novo aromatase synthesis that will overcome the inhibitory effect on estrogen production by aromatase inhibitors in premenopausal women. For that reason, in premenopausal women, using an aromatase inhibitor ***"alone"*** would not be effective in inhibiting estrogen production, and another agent to prevent the rise in endogenous gonadotropins is required. GnRH analogues (GnRH agonists or antagonists), as well as exogenous sex steroids are expected to be effective agents in blocking the endogenous rise in gonadotropins associated with aromatase inhibitor administration.

When aromatase inhibitors were used alone in premenopausal women with breast cancer, both failure of significant reduction of estrogen levels and elevated levels of gonadotropins were observed.[44-46] This was true even with the use of supratherapeutic levels of formestane.[47] However, third-generation aromatase inhibitors suppressed plasma estradiol concentrations more efficiently, although a near-complete suppression could not be achieved as is the case in postmenopausal women.[48] When the rise in endogenous gonadotropins was prevented (by GnRH agonist), aromatase inhibitors were found to be effective in suppressing circulating estrogen concentrations to levels comparable to those achieved in postmenopausal women.[49]

Evidence for Success of Aromatase Inhibitors for the Treatment of Endometriosis

It is not in the scope of this chapter to discuss medical treatment of endometriosis. Instead, the role of aromatase inhibitors in treating endometriosis-associated pain and infertility will be the focus of discussion.

Aromatase Inhibitors for Postmenopausal Women with Endometriosis

To our knowledge, the first case in the literature that reported the use of an aromatase inhibitor in treating endometriosis was in a postmenopausal woman. The patient had severe recurrent endometriosis and was previously operated three times including bilateral oophorectomy and resection of endometriosis. The patient had a 3-cm polypoid tumor in the vagina and severe pain. She continued to suffer from endometriosis-associated pain even after she underwent definitive treatment in the form of total hysterectomy with bilateral salpingo-oophorectomy. Obviously with the removal of both ovaries, the main source of estrogen production, there would be no role for GnRH agonist use. Treatment with progesterone for 4 months was not successful. The authors thought that peripheral and local estrogen production were the

underlying causes for activating her endometriotic lesions.The use of the aromatase inhibitor, anastrozole, proved successful in alleviating the woman's pain and inducing regression of the endometriotic lesions. After 9 months of treatment with anastrozole, the endometriotic lesion was reduced to a scar, and she had no pain.[50] In another report by Fatemi et al., a 55-year-old woman had a laparotomy due to subacute intestinal obstruction caused by endometriosis. After surgery, a mass about 4 to 8 cm was found in the rectovaginal septum. She was treated with the aromatase inhibitor, letrozole. After 1 year of treatment, she had no pain and the mass had shrunk to 1 cm.[51]

It is important to reiterate here that endometriosis is primarily a disease of women in the reproductive age group and postmenopausal women with endometriosis constitute a small fraction of women suffering from endometriosis-associated pain.

A recent review of the available literature on postmenopausal endometriosis found 32 case reports in Medline. The most commonly reported site for postmenopausal endometriosis was the ovaries. The risk of both recurrence and de novo occurrence of endometriosis was increased in women on hormone replacement therapy, in particular, estrogen only. The authors recommended that despite the rarity of endometriosis in postmenopausal women, it is important to be aware of this possibility, as well as the risk of ovarian cancer that is believed to be around 1%. For that reason, primary treatment should be surgical while medical treatment including aromatase inhibitors should be considered on an individual basis with very close follow up.[52]

Aromatase Inhibitors for Premenopausal Women with Endometriosis

Endometriosis-associated Pain

Unfortunately, many women with endometriosis-associated chronic pelvic pain are refractory to currently available medical treatments that aim at creating a pseudopregnant or hypoestrogenic state e.g. oral contraceptive pills, Depot Provera, oral progestins, and GnRH analogues.[53-55] In addition, significant side effects may cause patients to decline a potentially effective treatment, such as danazol for example, since the drug may have some androgenic activity.[56] On the other hand, conservative surgical excision of endometriosis usually provides significant pain relief. However, the degree and duration of pain relief following surgical treatment varies extensively among patients. Outcome of surgery depends on many factors including the experience of the surgeon, previous treatment history, and the use of adjuvant medical treatment.[57-60] Recurrence of endometriosis-associated pain unfortunately occurs in a good proportion of women following medical and/or surgical treatments. The last resort in many of these cases is definitive treatment by total hysterectomy and bilateral salpingo-oophorectomy. Even after this definitive treatment, pelvic pain has been reported in 3%–17% of women within a year following surgery.[61] For these reasons, the search continues for more effective treatments, particularly for women failing to respond to currently available treatment modalities. As explained earlier, the rationale for using aromatase inhibitors is scientifically plausible since suppressing the continued local estrogen production in endometriotic implants should make these lesions inactive. Local estrogen production in endometriosis would not be suppressed by currently available treatments such as GnRH analogues.[62-64] **Table 29-2** summarizes the clinical studies that have reported the use of aromatase inhibitors for endometriosis-associated pain.

In almost all those studies, one of two aromatase inhibitors belonging to the third generation (anastrozole or letrozole) has been used. High doses of calcium and vitamin D have been invariably administered to patients while receiving the aromatase inhibitors to minimize the risk of bone loss, particularly when long duration of treatment is considered. The concept of add-back of exogenous estrogen seems to be an exciting one that may reduce side effects without reducing the efficacy of pain relief. However, there is not much data in the literature to test this concept. Almost all reported patients who used an aromatase inhibitor were those who failed to respond to other currently available treatment modalities. In most of those studies, the response to aromatase inhibitors has been very encouraging with significant improvement in pain.

An adverse effect that has been reported with aromatase inhibitors use for endometriosis treatment in premenopausal women was the formation of ovarian cysts. Interestingly, significant pain relief occurred despite the formation of those cysts.[65] Formation of ovarian cysts seemed to have resulted from inadequate suppression of the rise in endogenous gonadotropins induced by withdrawal of estrogen negative feedback on the hypothalamus and/or pituitary. We have proposed another interesting mechanism through estrogen-mediated effects at the level of the anterior pituitary cells involving the local activin-inhibin-follistatin system. This system is responsible for an estrogen-selective modulation of the FSH

Table 29-2: Outline of reports on use of aromatase inhibitors in treating endometriosis-associated pain in premenopausal women

Study (year)	*Study design*	*Aromatase inhibitor used*	*Dose*	*Duration of treatment (months)*	*Adjuvant to suppress rise in endogenous gonadotropins*	*Number of women*	*Reference*
2004	Non-randomized	Letrozole	2.5 mg/day	6	Norethindrone 2.5 mg/day	10	Ailawadi et al [68]
2004	Case report	Letrozole	2.5 mg/day	3	Patient had bilateral oophorectomy	1	Razzi and Fava [69]
2004	Case report	Anastrozole	1 mg/day	6	Prometrium 200 mg/day	2	Shippen and West[70]
2004	Randomized trial Vs. GnRH agonist alone	Anastrozole	1 mg/day	6	GnRH agonist, goserlin 3.6 mg	97	Soysal et al. [71]
2005	Non-randomized	Anastrozole	0.25 mg/day (vaginally)	6	Non reported	10	Hefler et al [72]
2005	Case series	Anastrozole	1 mg/day	6	Oral contraceptive pills (Ethinyl Estradiol 20 microgram and Levonorgestrel 0.1 mg)	15	Amsterdam et al [73]
2007	Case report	Exemestane then Letrozole	Letrozole 2.5 mg/day	Less than 3 months	Patient had already bilateral oophorectomy	1	Mousa et al. [74]
2007	Case series	Letrozole	2.5 mg/day	About 3	desogestrel 0.075 mg	12	Remorgida et al. [75]
2009	Case series	-Letrozole for 4 patients -Anastrozole for one patient	-Letrozole 2.5 mg/day -Anastrozole 1mg/day	6	None reported	4	Verma abd Konje [76]

(but not LH) production by the anterior pituitary that is independent of GnRH.[66]

Using an aromatase inhibitor to treat other problems associated with endometriosis such as adhesions, has been tried but without success. In a recent case report anastrozole was found to be unsuccessful for treatment of endometriosis causing ureteral obstruction leading to hydronephrosis. A period of fifteen months of anastrozole treatment (1mg/day) did not improve renal function, and surgical intervention was required to alleviate pressure on the kidneys.[67]

Endometriosis-associated Infertility

The treatment of endometriosis-associated infertility is beyond the scope of this chapter and is discussed elsewhere. Here, we discuss the particular role of aromatase inhibitors in helping infertile women achieve pregnancy. There are different theories for endometriosis-associated infertility including ovulatory dysfunction, problems with the interaction between sperm and oocytes, and endometrial dysfunction, as well as interference with tubal motility or patency caused by pelvic adhesions. Aromatase inhibitors are believed to have the following roles in endometriosis-associated infertility:

1. Suppressing endometriotic lesions
2. Ovarian stimulation agents

1. **Suppressing endometriotic lesions:** As discussed earlier, there is evidence for the success of aromatase inhibitors in suppressing endometriosis and alleviating endometriosis-associated pain. Whether endometriosis suppression before infertility treatment improves the outcome of such treatment or not is still controversial. A recent report found combined down-regulation by an aromatase inhibitor and GnRH agonist to result in favorable IVF-ET outcome in women with ***"endometriomas"***. In this study, 20 women received the aromatase inhibitor anastrozole 1 mg daily for about 10 weeks with GnRH agonist depot (three doses of goserelin 3.6 mg every 4 weeks). During the combined down-regulation, the ***"endometriomal"*** volume and the serum CA125 level decreased by 29% (3-39%) and 61% (21-74%), respectively. Ovarian stimulation started on day 70 following combined down-regulation. In the IVF/ICSI cycle, the number of oocytes retrieved was 7.5

(6.0-10.0) and the fertilization rate was 78% (38-100%). Nine patients (45%) conceived, five (25%) had a clinical pregnancy, and three (15%) delivered healthy children (two singletons and one twin).[77] Despite the favorable outcome regarding the significant regression of endometriomas and reduction in CA125 levels, as well as acceptable IVF-ET outcomes, the study suffered from significant drawbacks, namely the small sample size and lack of a control group.

2. **Ovarian stimulation agents:** To our knowledge, there are no studies in the literature that looked at aromatase inhibitors as an ovarian stimulation agent exclusively in women with endometriosis. After we reported the success of an aromatase inhibitor in ovarian stimulation,[7-12] several other investigators confirmed our observations.[78-80] In those studies, women with endometriosis-associated infertility were included with women with other infertility factors, but were not analyzed separately.

In addition to the obvious value associated with low estrogen levels achieved during ovarian stimulation with aromatase inhibitors that might be of benefit in an estrogen-dependent disease such as endometriosis, we propose another interesting mechanism. The estrogen receptor subtype beta (ERb) is the predominantly expressed estrogen receptor in endometriotic tissues.[81] Contrary to the estrogen receptor subtype alpha (ERa) that is ***up***-regulated in the presence of ***low*** estrogen levels, the ERb is ***down***-regulated in ***low*** estrogenic milieu.[82] Low estrogen levels and the local hypo-estrogenic milieu expected with aromatase inhibitor use during ovarian stimulation might help suppression of endometriosis through an effect mediated by down-regulated ERb.

The most commonly used oral ovulation agent, clomiphene citrate has an agonistic effects on the ERb . In addition, the high circulating estradiol levels associated with clomiphene citrate treatment should upregulate ERb. Of historical interest, older literature dating back to the discovery and early use of clomiphene citrate in clinical practice recommended against the use of clomiphene citrate in women with endometriosis. Particularly, the presence of endometriomas was suggested as a contraindication for using clomiphene citrate as an ovarian stimulation agent.[83] An interesting study[84] found endometriosis in significant number of women (about two thirds) who had been treated by clomiphene citrate for several cycles without achievement of pregnancy. More recently, we reported treatment with clomiphene to significantly reduce the chance of pregnancy in women with endometriosis when compared to timed intercourse without clomiphene citrate treatment. In a cohort of 271 women with surgically-diagnosed endometriosis, after conservative endometriosis surgery, women were given the option of trying on their own with timed intercourse or receiving ovarian stimulation with clomiphene citrate. A total of 193 couples opted for timed intercourse without further intervention, while 78 preferred trying ovarian stimulation with clomiphene and timed intercourse. After controlling for stage of endometriosis, age and duration of infertility, clomiphene citrate treatment was associated with significantly lower clinical pregnancy rates compared to spontaneous pregnancy achieved by timed intercourse without ovarian stimulation.[85] In addition, the beneficial role of clomiphene ovarian stimulation in ovulatory infertility, particularly unexplained infertility, found to be minimal and has been questioned.[86] This could be simply because many women with unexplained infertility may have undiagnosed underlying endometriosis, especially with the recent trend towards less frequent use of diagnostic laparoscopy in evaluating infertility factors

Aromatase Inhibitors to Prevent Flare Associated with GnRH Agonist

An important potential benefit from aromatase inhibitors during the management of endometriosis is to prevent the estrogen flare associated with the initiation of GnRH agonist treatment. As explained above, GnRH agonist-induced hypoestrogenism is a successful treatment for endometriosis-associated pain and other estrogen-dependant disorders e.g. leiomyomas. However, a problem associated with GnRH agonist treatment is the initial flare-up of endogenous gonadotropins with subsequent increase in estradiol secretion by the ovaries and elevation in the circulating estradiol levels. This estrogen flare up usually lasts about one week before full suppression of the pituitary is achieved leading to the desired hypoestrogenic state.[87]

The flare of estradiol associated with GnRH agonist results in undesired adverse effects including irregular endometrial bleeding, accentuated pelvic pain or even potential growth of estrogen-dependent tumors. Moreover, incidents of grave complications, such as intestinal obstruction and perforation due to sudden growth of intestinal endometriosis have been reported.[88, 89]

A recent preliminary study found that the use of the aromatase inhibitor, letrozole, when given at a dose of 2.5 mg/day starting on the day of GnRH agonist administration was successful in alleviating the initial estrogen flare up. Letrozole was administered for five days and successfully prevented any rise in estradiol levels in all 14

patients included in the study (GnRH agonist was administered in 9 patients for endometriosis and 5 for leiomyomas).[90]

Aromatase Inhibitors for Adenomyosis

Adenomyosis or endometriosis interna (endometriosis of the uterine wall) is frequently associated with significant debilitating symptoms including pelvic pain and excessive menstrual bleeding. The exact prevalence of this condition is unclear. The diagnosis and management of adenomyosis are still significant challenges to clinicians. Hysterectomy is often the ultimate treatment because conservative treatments to prevent pain or bleeding while retaining fertility are extremely difficult.[91] Recently, there have been reports of significant aromatase activity in uterine adenomyosis.[92] Therefore, the inhibition of estrogen production by an aromatase inhibitor is a logical approach. A recent case report describes a 34 year old woman with adenomyosis who had severe clinical symptoms and a strong desire to retain fertility. After the failure of adequate response to GnRH agonist and danazol treatment, a concomitant treatment of an aromatase inhibitor (anastrozole 1 mg daily) and a GnRH agonist was found effective. The patient's symptoms were almost eradicated after four months of treatment and remained under contol for six months after anastrozole was discontinued while continuing administration of GnRH agonist.[93]

Conclusion

We hope that the above review succeeded in clarifying the answers to the following questions:

Is there a sound scientific hypothesis to support the success of aromatase inhibitors in managing endometriosis?

It seems that the answer to this question is yes and that there is enough scientific evidence to support aromatase inhibitors as a new tool in the fight against endometriosis-associated health problems. This is based on the significant expression of aromatase and synthesis of local estrogen inside the endometriotic tissues, suppression of which might have a positive effect on alleviating endometriosis-associated symptoms of pain and infertility.

What is the existing clinical evidence that supports such novel application?

Despite the lack of large properly designed randomized trials, the available evidence is strong enough to conclude that aromatase inhibitors are useful ase an alternative treatment in managing endometriosis. This is particularly true when considering:

- First: the wide safety profile and high tolerability of the third-generation aromatase inhibitors
- Second: the significant success in reported cases of women with severe endometriosis-associated symptoms who failed to respond to currently available treatment modalities

Is there a difference among various aromatase inhibitors for such application?

We do not believe there is enough evidence for or against the presence of significant difference among aromatase inhibitors. Even though there is some evidence for possible superiority of one aromatase inhibitor over another when it comes to potency, there is not enough evidence that such difference would translate into a significant difference in clinical efficiency

What is the optimum regimen for managing endometriosis with aromatase inhibitors?

At the present time, there is no answer to this question. We believe that an important question to consider is what would be the optimum and most cost-effective approach to prevent the rise in endogenous gonadotropins associated with aromatase inhibitors use in premenopausal women. In postmenopausal women, we believe that a combined regimen of an aromatase inhibitor together with hormone replacement (estrogen and progesterone) as add-back therapy seems to be the optimum when it comes to preventing drawbacks associated with long-term hypoestrogenism at the level of the bones, and blood lipids, as well as menopausal symptoms e.g. vaginal dryness and hot flashes.

References

1. Noble, L.S., Simpson, E.R., Johns, A., Bulun, S.E., 1996. Aromatase expression in endometriosis. J. Clin. Endocrinol. Metab. 81, 174–179.
2. Noble, L.S., Takayama, K., Putman, J.M., Johns, D.A., Hinshelwood, M.M., Agarwal, V.R., Zhao, Y., Carr, B.R., Bulun, S.E., 1997. Prostaglandin E2 stimulates aromatase expression in endometriosis-derived stromal cells. J. Clin. Endocrinol. Metab. 82, 600–606.
3. Zeitoun K, Takayama K, Michael MD, Bulun SE. Stimulation of aromatase P450 promoter (II) activity in endometriosis and its inhibition in endometrium are regulated by competitive binding of SF-1 and COUP-TF to the same cis-acting element. Mol Endocrinol 1999;13:239–53.
4. Kitawaki J, Noguchi T, Amatsu T, Maeda K, Tsukamoto K, Yamamoto T, Fushiki S, Osawa Y, Honjo H. 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.
7. Mitwally MFM, Casper RF. Aromatase Inhibition: a novel method of ovulation induction in women with polycystic ovarian syndrome. Reprod Technol, 2000;10:244-247.
8. Mitwally MFM, Casper RF. Use of an aromatase inhibitor for induction of ovulation in patients with an inadequate response to clomiphene citrate. Fertil Steril,2001;75:305-309.
9. Mitwally MFM, Casper RF. Aromatase inhibition improves ovarian response to follicle-stimulating hormone in poor responders. Fertil Steril,2002;774:776-780.
10. Mitwally MF, Casper RF. Aromatase inhibition reduces gonadotrophin dose required for controlled ovarian stimulation in women with unexplained infertility. Hum Reprod,2003;188:1588-1597.
11. Mitwally MF, Casper RF. Aromatase inhibition reduces the dose of gonadotropin required for controlled ovarian hyperstimulation. J Soc Gynecol Investig,2004;11:406-415
12. Mitwally MFM, Casper RF. Single dose administration of the aromatase inhibitor, letrozole: a simple and convenient effective method of ovulation induction. Fertil Steril,2005;83:229-231.
13. B.R. Carr, Disorders of the ovaries and female reproductive tract. In: J.D. Wilson, D.W. Foster, H.M. Kronenberg and P.R. Larsen, Editors, *Williams textbook of endocrinology* (9th ed.), WB Saunders, Philadelphia (1998), pp. 751–817.
14. R. Barbieri and K. Ryan, The menstrual cycle. In: K. Ryan, R. Berkowitz, R. Barbieri and A. Dunaif, Editors, *Kistner's gynecology and women's health* (7th ed.), Mosby, St Louis (1999), pp. 32–34.
15. E. R. Simpson. Sources of estrogen and their importance. The Journal of Steroid Biochemistry and Molecular Biology. Volume 86, Issues 3-5, September 2003, Pages 225-230
16. L.R. Nelson and S.E. Bulun, Estrogen production and action, *J Am Acad Dermatol* 45 (2001) (Suppl), pp. S116–S124
17. Cole PA, Robinson CH. Mechanism and inhibition of cytochrome P-450 aromatase. J Med Chem 1999; 33:2933-44
18. Buzdar A, Howell A. Advances in aromatase inhibition: clinical efficacy and tolerability in the treatment of breast cancer. Clin Cancer Res 2001; 7:2620–35
19. Lang M, Batzl C, Furet P, Bowman R, Häusler A, Bhatnagar AS (1993) Structure-activity relationships and binding model of novel aromatase inhibitors. J Steroid Biochem Mol Biol 44:421–428.
20. Sainsbury R 2004 Aromatase inhibition in the treatment of advanced breast cancer: is there a relationship between potency and clinical efficacy? *British Journal of Cancer* 90 1733–1739.
21. Bhatnagar AS, Brodie AMH, Long BJ, Evans DB, Miller WR (2001) Intracellular aromatase and its relevance to the pharmacological efficacy of aromatase inhibitors. J Steroid Biochem Mol Biol 76:199–202
22. Bhatnagar AS, Häusler A, Schieweck K, Lang M, Bowman R (1990) Highly selective inhibition of estrogen biosynthesis by CGS 20267, a new non-steroidal aromatase inhibitor. J Steroid Biochem Mol Biol 37:1021–1027
23. Miller WR (1999) Biology of aromatase inhibitors: pharmacology/endocrinology within the breast. Endocr Relat Cancer 6:187–195
24. Bhatnagar AS, Häusler A, Schieweck K, Lang M, Bowman R (1990) Highly selective inhibition of estrogen biosynthesis by CGS 20267, a new non-steroidal aromatase inhibitor. J Steroid Biochem Mol Biol 37:1021–1027
25. Demers LM (1994) Effects of fadrozole (CGS 16949A) and letrozole (CGS 20267) on the inhibition of aromatase activity in breast cancer patients. Breast Cancer Res Treat 30:95–102
26. Lønning P, Pfister C, Martoni A, Zamagni C (2003) Pharmacokinetics of third-generation aromatase inhibitors. Semin Oncol 30(Suppl 14):23–32
27. Dowsett M, Pfister CU, Johnston SRD, Houston SJ, Miles DW, Verbeek JA, Smith IE (1997) Pharmacokinetic interaction between letrozole and tamoxifen in postmenopausal patients with advanced breast cancer. The Breast 6:245
28. J. Geisler, S. Detre, H. Berntsen, L. Ottestad, B. Lindtjørn, M. Dowsett and P.E. Lønning, Influence of neoadjuvant anastrozole (Arimidex) on intratumoral estrogen levels and proliferation markers in patients with locally advanced breast cancer, *Clin. Cancer Res.* 7 (2001), pp. 1230–1236.
29. J. Geisler, B. Haynes, G. Anker, M. Dowsett and P.E. Lønning, Influence of letrozole (Femara) and anastrozole (Arimidex) on total body aromatization and plasma estrogen levels in postmenopausal breast cancer patients evaluated in a randomized, cross-over-designed study, *J. Clin. Oncol.* 20 (2002), pp. 751–757.
30. J. Geisler, S. Helle, D. Ekse, N. Duong, D. Evans and P. Lonning, Letrozole (Femara) causes potent suppression of breast cancer tissue estrogen levels in the neoadjuvant setting, *J. Clin. Oncol.* 24 (2006), p. 570s.
31. M . Khazaei , A . Montaseri , R . Casper. Letrozole stimulates the growth of human endometrial explants cultured in three-dimensional fibrin matrix . Fertil Steril. 2008 Apr 8. Epub ahead of print
32. E. Bajetta, L. Ferrari, L. Celio, L. Mariani, R. Miceli and A. Di Leo *et al.*, The aromatase inhibitor letrozole in advanced breast cancer: effects on serum insulin-like growth factor (IGF)-I and IGF-binding protein-3 levels, *J Steroid Biochem Mol Biol* 63 (1997), pp. 261–267.
33. F. Talavera, R.K. Reynolds, J.A. Roberts and M.J. Menon, Insulin-like growth factor I receptors in normal and neoplastic human endometrium, *Cancer Res* 50 (1990), pp. 3019–3024.
34. L.J. Murphy, L.C. Murphy and H.G. Friesen, Estrogen induces insulin-like growth factor-I expression in rat uterus, *Mol Endocrinol* 1 (1987), pp. 445–450.
35. Geisler J & Lønning PE 2005 Aromatase inhibition: transaltion into a successful therapeutic approach. *Clinical Cancer Research* 11 2809–2821.
36. Tominaga T, Adachi I, Sasaki Y, Tabei T, Ikeda T, Takatsuka Y, Toi M, Suwa T & Ohashi Y 2003 Double-blind randomised trial comparing the non-steroidal aromatase inhibitors letrozole and fadrozole in postmenopausal women with advanced breast cancer. *Annals of Oncology* 14 62–70.
37. The discovery and mechanism of action of letrozole. Ajay S. Bhatnagar. Breast Cancer Research and Treatment, 2007, 105, Suppl. 1:2-17

38. R. Ponzone, P. Mininanni, E. Cassina, F. Pastorino, and P. Sismondi. Aromatase inhibitors for breast cancer: different structures, same effects? Endocr. Relat. Cancer, March 1, 2008; 15(1): 27 - 36
39. Harold J. Burstein. Aromatase inhibitor-associated arthralgia syndrome. *The Breast, Volume 16, Issue 3, June 2007, Pages 223-234*
40. Reid DM, Doughty J, Eastell R, Heys SD, Howell A, McCloskey EV, Powles T, Selby P, Coleman RE. Guidance for the management of breast cancer treatment-induced bone loss: a consensus position statement from a UK Expert Group. Cancer Treat Rev. 2008;34 Suppl 1:S3-18. Epub 2008 Jun 2.
41. Wu M, Wang C, Lin C, Chen L, Chang W, Tsai S. Distinct regulation of cyclooxygenase-2 by interleukin-1{beta} in normal and endometriotic stromal cells. J Clin Endocrinol Metab 2005;90(1):286 –95.
42. Ota H, Igarashi S, Sasaki M, Tanaka T. Distribution of cyclooxygenase-2 in eutopic and ectopic endometrium in endometriosis and adenomyosis. Hum Reprod 2001;16:561–6.
43. Moudgal NR, Shetty G, Selvaraj N, Bhatnagar AS. Use of a specific aromatase inhibitor for determining whether there is a role for oestrogen in follicle/oocyte maturation, ovulation and preimplantation embryo development. J Reprod Fertil Suppl 1996;50:69–81.
44. Santen RJ, Samojlik E, Wells SA. Resistance of the ovary to blockade of aromatization with aminoglutethimide. J Clin Endocrinol Metab 1980;51:473–7.
45. Harris AL, Dowsett M, Jeffcoate SL, McKinna JA, Morgan M, Smith IE. Endocrine and therapeutic effects of aminoglutethimide in premenopausal patients with breast cancer. J Clin Endocrinol Metab 1982;55:718–22.
46. Wander HE, Blossey HC, Nagel GA. Aminoglutethimide in the treatment of premenopausal patients with metastatic breast cancer. Eur J Cancer Clin Oncol 1986;22:1371– 4.
47. Stein RC, Dowsett M, Hedley A, Davenport J, Gazet JC, Ford HT, et al. Treatment of advanced breast cancer in postmenopausal women with 4-hydroxyandrostenedione. Cancer Chemother Pharmacol 1990;26:75–8.
48. Wouters W, De Coster R, Krekels M, van Dun J, Beerens D, Haelterman C, et al. R 76713, a new specific non-steroidal aromatase inhibitor. J Steroid Biochem 1989;32:781– 8.
49. Stein RC, Dowsett M, Hedley A, Gazet JC, Ford HT, Coombes RC. The clinical and endocrine effects of 4-hydroxyandrostenedione alone and in combination with goserelin in premenopausal women with advanced breast cancer. Br J Cancer 1990;62:679–83.
50. Takayama K, Zeitoun K, Gunby RT, Sasano H, Carr BR, Bulun SE. Treatment of severe postmenopausal endometriosis with an aromatase inhibitor. Fertil Steril. 1998;/69(4):709_13.
51. Fatemi HM, Al-Turki HA, Papanikolaou EG, Kosmas L, DeSutter P, Devroey P. Successful treatment of an aggressive recurrent postmenopausal endometriosis with an aromatase inhibitor. Reprod Biomed Online. 2005;/11(4):/455_7.
52. Oxholm, Dorthe, Knudsen, Ulla Breth, Kryger-Baggesen, Niels and Ravn, Pernille(2007)'Postmenopausal endometriosis', Acta Obstetricia et Gynecologica Scandinavica,86:10,1158-1164
53. Vercellini P, Trespidi L, Colombo A. A gonadotropin-releasing hormone agonist versus a low-dose oral contraceptive for pelvic pain associated with endometriosis. Fertil Steril 1993;60:75–9.
54. Waller KG, Shaw RW. Gonadotropin-releasing hormone analogues for the treatment of endometriosis: long-term follow-up. Fertil Steril 1993; 59:511–5.
55. Vercellini P, Trespidi L, DeGiorgi O, Cortesi I, Parazzini F, Crosignani PG. Endometriosis and pelvic pain. Relation to disease stage and localization. Fertil Steril 1996;65:299 – 304.
56. Kauppila A. Changing concepts of medical treatment of endometriosis. Acta Obstet Gynecol Scand 1993;72:324 – 36.
57. Vercellini P, Fedele L, Bianchi S, Candiani GB. Pelvic denervation for chronic pain associated with endometriosis: fact or fancy? Am J Obstet Gynecol 1991;165:745–9.
58. Wilson ML, Farquhar CM, Sinclair OJ, Johnson NP. Surgical interruption of pelvic nerve pathways for primary and secondary dysmenorrhoea. Cochrane Database Syst Rev 2000;(2):CD001896.
59. Gambone JC, Mittman BS, Munro MG, Scialli AR, Winkel CA. Consensus statement for the management of chronic pelvic pain and endometriosis:proceedings of an expert-panel consensus process. Fertil Steril 2002;78:961–72.
60. Olive DL, Pritts EA. The treatment of endometriosis: a review of the evidence. Ann NY Acad Sci 2002;955:360 – 72.
61. Vercellini P, De Giorgi O, Pisacreta A, Pesole AP, Vicentini S, Crosignani PG. Surgical management of endometriosis. Baillieres Best Pract Res Clin Obstet Gynaecol 2000;14:501–23.
62. Shippen ER, West WJ Jr. Successful treatment of severe endometriosis in two premenopausal women with an aromatase inhibitor. Fertil Steril 2004;81:1395– 8.
63. Takayama K, Zeitoun K, Gunby RT, Sasano H, Carr BR, Bulun SE. Treatment of severe postmenopausal endometriosis with an aromatase inhibitor. Fertil Steril 1998;69:709 –13.
64. Razzi S, Fava A, Sartini A, De Simone S, Cobellis L, Petraglia F. Treatment of severe recurrent endometriosis with an aromatase inhibitor in a young ovariectomised woman. Br J Obstet Gynaecol 2004;111:182– 4.
65. Remorgida V, Abbamonte HL, Ragni N, Fulcheri E, Ferrero S. Letrozole and norethisterone acetate in rectovaginal endometriosis. Fertil Steril. 2007 Sep;88(3):724-6. Epub 2007 Feb 28.
66. Mitwally MF, Casper RF, Diamond MP. Oestrogen-selective modulation of FSH and LH secretion by pituitary gland. Br J Cancer. 2005 Jan 31;92(2):416-7.
67. Bohrer J, Chen CC, Falcone T. Persistent bilateral ureteral obstruction secondary to endometriosis despite treatment with an aromatase inhibitor. Fertil Steril. 2008;90(5): 2004.e7-9. Epub 2008 Jun 16.
68. Ailawadi R, Jobanputra S, Kataria M, Gurates B, Bulun SE. Treatment of endometriosis and chronic pelvic pain with letrozole and norethindrone acetate: a pilot study. Fertil Steril 2004;81:290–6.

69. Razzi S, Fava A. Treatment of severe recurrent endometriosis with an aromatase inhibitor in a young ovariectomised woman. BJOG 2004;81:290–6.
70. Shippen ER, West WJ Jr. Successful treatment of severe endometriosis in two premenopausal women with an aromatase inhibitor. Fertil Steril 2004;81:1395–8.
71. Soysal S, Soysal M, Ozer S, Gul N, Gezgin T. The effects of post-surgical administration of goserelin plus anastrazole compared to goserelin alone in patients with severe endometriosis: a prospective randomized trial. Hum Reprod 2004;19:160–7.
72. Hefler L, Grimm C, van Trotsenburg M, Nagele F. Role of the vaginally administered aromatase inhibitor anastrozole in women with rectovaginal endometriosis: a pilot study. Fertil Steril 2005;84:1033–6.
73. 85-22 Amsterdam LL, Gentry W, Jobanputra S, Wolf M, Rubin SD, Bulun SE. Anastrazole and oral contraceptives: a novel treatment for endometriosis. Fertil Steril 2005;84:300–4.
74. Mousa NA, Bedaiwy MA, Casper RF. Aromatase inhibitors in the treatment of severe endometriosis. Obstet Gynecol. 2007 Jun;109(6):1421-3.
75. Remorgida V, Abbamonte LH, Ragni N, Fulcheri E, Ferrero S. 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.
76. Verma A, Konje JC. Successful treatment of refractory endometriosis-related chronic pelvic pain with aromatase inhibitors in premenopausal patients. Eur J Obstet Gynecol Reprod Biol. 2009 Feb 20. [Epub ahead of print.]
77. Lossl K, Loft A, Freiesleben NL, Bangsbøll S, Andersen CY, Pedersen AT, Hartwell D, Andersen AN. Combined down-regulation by aromatase inhibitor and GnRH-agonist in IVF patients with endometriomas-A pilot study. Eur J Obstet Gynecol Reprod Biol. 2009 Mar 2. [Epub ahead of print.]
78. Healey S, Tan SL, Tulandi T, Biljan MM. Effects of letrozole on superovulation with gonadotropins in women undergoing intrauterine insemination. Fertil Steril,2003;806:1325-1329.
79. Cortinez A, De Carvalho I, Vantman D et al. Hormonal profile and endometrial morphology in letrozole-controlled ovarian hyperstimulation in ovulatory infertile patients. Fertil Steril 2005;83(1):110-115.
80. Fatemi HM, Kolibianakis E, Tournaye H et al. Clomiphene citrate versus letrozole for ovarian stimulation: a pilot study. Reprod Biomed Online,2003;75:543-546.
81. Harris HA. Mol Endocrinol. Estrogen receptor-beta: recent lessons from in vivo studies. 2007 Jan;21(1):1-13. Epub 2006 Mar 23.
82. Signaling regulation of genomic and nongenomic functions of estrogen receptors. Acconcia F, Kumar R.
83. Gabos P. Clomiphene citrate therapy and associated ovarian endometrial cysts. Obstet Gynecol. 1979 Jun;53(6):763-5.
84. Capelo FO, Kumar A, Steinkampf MP, Azziz R. Laparoscopic evaluation following failure to achieve pregnancy after ovulation induction with clomiphene citrate. Fertil Steril. 2003 Dec;80(6):1450-3.
85. M FM Mitwally, H Albuarki, M Ashraf, M P Diamond, M Abuzeid. Clomiphene reduces chance of pregnancy in infertile women with endometriosis following laparoscopic surgery. J Soc Gynecol Investig Vol. 13, No. 2 (Supplement), February 2006. Abstract 646: page 277A
86. Practice Committee of the American Society for Reproductive Medicine. Effectiveness and treatment for unexplained infertility. Fertil Steril. 2006 Nov;86(5 Suppl):S111-4.
87. Dupont A, Dupont P, Belanger A, Mailoux J, Cusan L, Labrie F. Hormonal and biochemical changes during treatment of endometriosis with the luteinizing hormone-releasing hormone (LH-RH) agonist D-Trp6,des-Gly-NH2(10). LH-RH ethylamide. Fertil Steril 1990;54: 227–32.
88. Saito S, Murakami T, Suzuki K, Terada Y, Fukushima K, Moriya T. Intestinal endometriosis complicated by ileal perforation after initiation of gonadotropin-releasing hormone agonist therapy. Fertil Steril 2007;88:969.e7–9.
89. Hall LLH, Malone JM, Ginsburg KA. Flare-up of endometriosis induced by gonadotropin-releasing hormone agonist leading to bowel obstruction. Fertil Steril 1995;64:1204–6.
90. Bedaiwy MA, Mousa NA, Casper RF. Aromatase inhibitors prevent the estrogen rise associated with the flare effect of gonadotropins in patients treated with GnRH agonists. Fertil Steril. 2009 Apr;91(4 Suppl):1574-7.
91. Fong YF, Singh K. Medical treatment of a grossly enlarged adenomyotic uterus with the levonorgestrel-releasing intrauterine system. Contraception 1999;60:173–5.
92. Kitawaki J, Noguchi T, Amatsu T, Maeda K, Tsukamoto K, Yamamoto T. Expression of aromatase cytochrome P450 protein and messenger ribonucleic acid in human endometriotic and adenomyotic tissue but not in normal endometrium. Biol Reprod 1997;57:514 –9.
93. Fuminori Kimura, Kentaro Takahashi, Koichi Takebayashi, Mutsuko Fujiwara, Nobuyuki Kita, Yoichi Noda, Nobuhiro Harada. Concomitant treatment of severe uterine adenomyosis in a premenopausal woman with an aromatase inhibitor and a gonadotropin-releasing hormone agonist. Fertility and Sterility_ Vol. 87, No. 6, June 2007