The American College of Obstetricians and Gynecologists
WOMEN'S HEALTH CARE PHYSICIANS

ACOG COMMITTEE OPINION

Number 738 • June 2018

(Replaces Committee Opinion Number 663, June 2016)

Committee on Gynecologic Practice

This Committee Opinion was developed by the American College of Obstetricians and Gynecologists' Committee on Gynecologic Practice.

INTERIM UPDATE: This Committee Opinion is updated as highlighted to clarify the use of letrozole for women with polycystic ovary syndrome.

Aromatase Inhibitors in Gynecologic Practice

ABSTRACT: Aromatase inhibitors have been used for the treatment of breast cancer, ovulation induction, endometriosis, and other estrogen-modulated conditions. For women with breast cancer, bone mineral density screening is recommended with long-term aromatase inhibitor use because of the risk of osteoporosis due to estrogen deficiency. Based on long-term adverse effects and ~~complication~~ safety data, when compared with tamoxifen, aromatase inhibitors are associated with a reduced incidence of thrombosis, endometrial cancer, and vaginal bleeding. For women with polycystic ovary syndrome, ~~and a body mass index greater than 30,~~ letrozole should be considered first-line therapy for ovulation induction because of the increased live birth rate compared with clomiphene citrate. Lifestyle changes that result in weight loss should be strongly encouraged. Aromatase inhibitors are a promising therapeutic option that may be helpful for the management of endometriosis-associated pain in combination therapy with progestins.

Conclusions and Recommendations

The American College of Obstetricians and Gynecologists supports the following recommendations and conclusions:

- For women with breast cancer, bone mineral density screening is recommended with long-term aromatase inhibitor use because of the risk of osteoporosis due to estrogen deficiency.
- Based on long-term adverse effects and safety data, when compared with tamoxifen, aromatase inhibitors are associated with a reduced incidence of thrombosis, endometrial cancer, and vaginal bleeding.
- For women with polycystic ovary syndrome, ~~and a body mass index (BMI) greater than 30,~~ letrozole should be considered first-line therapy for ovulation induction because of the increased live birth rate compared with clomiphene citrate. Lifestyle changes that result in weight loss should be strongly encouraged.
- For women with unexplained infertility (regular menstrual cycles, all known male or female factors excluded), a large multicenter study demonstrated that ovulation induction with letrozole resulted in lower live birth rates and multiple gestation rates compared with gonadotropins; however, live birth and multiple gestation rates did not differ significantly between ovulation induction with letrozole compared with clomiphene citrate.
- Aromatase inhibitors are a promising therapeutic option that may help manage endometriosis-associated pain in combination therapy with progestins.

This Committee Opinion revision provides updated information on the use of aromatase inhibitors in breast cancer, ovulation induction, and endometriosis, and long-term follow-up data from relevant studies. Aromatase is a microsomal cytochrome P450 hemoprotein-containing enzyme (P450arom, the product of the *CYP19* gene), and it is widely expressed in tissues, such as brain, breast, placenta, ovary, testes, endometrium, skin, bone, and fat. Within these tissues, aromatase mediates the conversion of androstenedione to estrone and the conversion of testosterone to estradiol in situ. Thus, for tissues that express this enzyme, conversion of circulating androgens from an adrenal or ovarian source will significantly increase the in situ estrogen concentrations and provide these tissues with a proliferative advantage. In postmenopausal women, inhibitors of the

aromatase enzyme reduce circulating estradiol levels from 20 pg/mL to less than 1–3 pg/mL (1, 2). Based on these varying effects, aromatase inhibitors have been used for the treatment of breast cancer, ovulation induction, endometriosis, and other estrogen-modulated conditions.

Three aromatase inhibitors are currently commercially available in the United States. Exemestane is a steroid-derived aromatase inhibitor that binds irreversibly to aromatase and permanently inactivates the available enzyme. Letrozole and anastrozole are reversible inhibitors of aromatase that compete with androgens for aromatase binding sites. All three aromatase inhibitors are available in pill form and appear to have similar clinical efficacy despite differences in pharmacologic properties.

Breast Cancer

Because estrogen is theorized to play an important role in the pathogenesis and proliferation (or growth) of breast cancer, one treatment strategy for hormone-sensitive breast cancer is to decrease circulating estrogen levels. Aromatase inhibitors are one class of drugs used for this purpose. Additional guidance on the management of gynecologic issues in women with breast cancer can be found in the American College of Obstetricians and Gynecologists' Practice Bulletin No. 126, *Management of Gynecologic Issues in Women With Breast Cancer* (3).

Postmenopausal Women

In postmenopausal women, aromatase inhibitors were first introduced for the treatment of advanced breast cancer. The early success of studies led to clinical trials of aromatase inhibitors in breast cancer patients with resectable, estrogen receptor-positive tumors. The largest of these trials has compared anastrozole alone with tamoxifen alone, or the combination, (4) as adjuvant treatment in women with early breast cancer after surgical resection. The 10-year follow-up study results demonstrated that anastrozole is better than tamoxifen in the prevention of recurrence of breast cancer in postmenopausal women with early-stage hormone receptor-positive tumors (5). Additional studies have shown the effectiveness of aromatase inhibitors in other breast cancer clinical scenarios, including ductal carcinoma in situ (6). Specific guidelines can be accessed at National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (7) and the 2014 American Society of Clinical Oncology Clinical Practice Guidelines (8).

Premenopausal Women

Aromatase inhibitors should not be used alone in women with breast cancer who have preserved ovarian function. There is a growing body of evidence that supports effective use of aromatase inhibitors with ovarian suppression in select populations, such as women who remained premenopausal after completing chemotherapy and who were at sufficient risk of recurrence to warrant adjuvant chemotherapy (9). Aromatase inhibitors should be avoided in premenopausal women who have chemotherapy-induced amenorrhea with breast cancer because ovarian function can resume after the initiation of an aromatase inhibitor regimen, which renders the treatment ineffective (10, 11) Numerous trials have evaluated combinations of therapies with aromatase inhibitors alone or with other agents and, thus, gynecologists who work with breast cancer patients and survivors should become familiar with the patient's specific protocol in order to best provide appropriate care and support.

Chemoprevention of Breast Cancer

Studies have shown the effectiveness of aromatase inhibitors for the prevention of breast cancer in high-risk patients (12). The U.S. Preventive Services Task Force recommends that clinicians engage in shared, informed decision making with women who are at increased risk of breast cancer about medications to reduce their risk; the U.S. Preventive Services Task Force recommends against the routine use of medications, such as tamoxifen or raloxifene, for risk reduction of primary breast cancer in women who are not at increased risk of breast cancer (13).

Adverse Effects

The short-term and long-term adverse effects of aromatase inhibitors in postmenopausal women are related to lack of estrogen action at aromatase-targeted tissue sites. These adverse effects include hot flushes, vaginal dryness, arthralgia, decreased bone mineral density, and an increased fracture rate (4). Nonhormonal methods, such as moisturizers, should be considered as first-line therapy for women with localized vulvar or vaginal symptoms (3). A case–control study of women with breast cancer who used vaginal estrogen did not show an increase in recurrence with local estrogen use compared with nonuse (14). The use of vaginal estrogen in women with a history of estrogen-dependent tumors may be considered in symptomatic women after discussion of quality of life and risks and benefits (15). The entire medical team, including the treating medical oncologist, should be included in this discussion (15).

For women with breast cancer, bone mineral density screening is recommended with long-term aromatase inhibitor use because of the risk of osteoporosis due to estrogen deficiency. The National Comprehensive Cancer Network recommends baseline and periodic follow-up bone density testing for women treated with aromatase inhibitors (7). To reduce the risk of osteoporosis in high-risk patients, bisphosphonates are typically co-administered to patients during long-term treatment with aromatase inhibitors (16). Potential risks of bisphosphonates reported after marketing include

osteonecrosis of the jaw, seizures, atypical fractures of the femoral shaft, and esophageal cancer. A precise understanding of the true risk of these events has been difficult to determine because of the lack of data on the incidence of these problems in the general population. Although rare cases of osteonecrosis of the jaw have been reported in patients using bisphosphonates for osteoporosis, it has been seen most commonly after dental extractions in those being treated with large intravenous doses of bisphosphonates in association with supportive cancer therapy (17). Use of bisphosphonates for this population may require a consultation with a specialist. More recently, an anti-RANK-Ligand (Receptor Activator of Nuclear Factor κ B ligand) antibody has been used to prevent bone loss in women receiving aromatase inhibitors (18). The RANK-Ligand is the essential mediator of osteoclast activity and bone resorption, and is produced by bone cells in the skeleton (18, 19).

Based on long-term adverse effects and safety data, when compared with tamoxifen, aromatase inhibitors are associated with a reduced incidence of thrombosis, endometrial cancer, and vaginal bleeding (20, 21). Aromatase inhibitors have been shown to have adverse effects on the cardiovascular system and lipid profiles compared with tamoxifen (20, 21). Most of those who discontinue the use of aromatase inhibitors do so because of musculoskeletal symptoms, fatigue, forgetfulness, or sleep disturbances (20–22).

Ovulation Induction

The gonadotropin-stimulating action of letrozole has been used off-label in the treatment of patients with ovulatory dysfunction, such as polycystic ovary syndrome, and to increase follicular recruitment in women who are already ovulatory (23–25). If prescribing letrozole, the starting dose is 2.5 mg/day for 5 days typically starting on day 3, 4, or 5 after a spontaneous menses or progestin-induced bleed. If ovulation does not occur, the dose can be increased to 5 mg/day for 5 days with a maximum dose of 7.5 mg/day. Doses higher than 7.5 mg/d have been associated with thinning of the endometrium as seen with clomiphene citrate (26).

For women with unexplained infertility (regular menstrual cycles, all known male or female factors excluded), a large multicenter study demonstrated that ovulation induction with letrozole resulted in lower live birth rates and multiple gestation rates compared with gonadotropins. Although letrozole and clomiphene citrate demonstrated similar live birth and multiple gestation rates, the study was not powered to detect a difference between these two medications (27). Further trials are needed to determine which is better for the treatment of unexplained infertility.

Letrozole also has been used for ovulation induction for women with polycystic ovary syndrome (PCOS). In an early meta-analysis of four published trials that included 662 women with PCOS, pregnancy rates were similar between women treated with clomiphene citrate and women treated with letrozole (relative risk, 1.02; 95% confidence interval, 0.83–1.26) (28). However, in a more recent randomized controlled trial, letrozole was more effective than clomiphene citrate with a higher live birth rate (27.5% versus 10.1%. $P=.007$), and cumulative ovulation rate (61.7% versus 48.3%, $P<.001$) (29). ~~In women with a BMI greater than or equal to 30.3, ovulation induction with letrozole resulted in a higher live birth rate when compared with clomiphene citrate (29, 30).~~ Therefore, for women with PCOS, ~~and a BMI greater than 30,~~ letrozole should be considered first-line therapy for ovulation induction because of the increased live birth rate compared with clomiphene citrate. Although ovulation induction is very effective, it is important to recognize that for obese women with PCOS, lifestyle changes that result in weight loss should be strongly encouraged. A 7% decrease in BMI may result in spontaneous ovulation and avoid the need for therapy for ovulation induction (30, 31). For an obese patient, lifestyle changes should always be encouraged; weight changes as little as 5% of body weight may improve reproductive function (30). More information on polycystic ovary syndrome can be found in the American College of Obstetricians and Gynecologists' Practice Bulletin No. 194, *Polycystic Ovary Syndrome* (32).

A number of studies have shown that letrozole appears to have a role in the treatment of clomiphene-resistant patients; 50–80% of clomiphene nonresponders have been shown to ovulate after using letrozole (33–35). Some of these studies have raised concerns about this off-label use because letrozole may disrupt the normal aromatase activity in tissues during early fetal development and can be potentially teratogenic if administered inadvertently during early pregnancy. Although studies have demonstrated that newborns whose mothers achieved pregnancy by using letrozole for ovulation induction showed no significant difference in rates of congenital malformations compared with those newborns whose mothers used the clomiphene citrate treatment, (29, 36) long-term data are needed to confirm this finding. It should be noted that letrozole and clomiphene citrate are pregnancy category X. When prescribing letrozole for ovulation induction, patients should be counseled that unlike clomiphene citrate, letrozole is not approved by the U.S. Food and Drug Administration for ovulation induction.

Endometriosis

Aromatase inhibitors are a promising therapeutic option that may help manage endometriosis-associated pain in combination therapy with progestins. The recent demonstration that aromatase is expressed at higher levels in endometriosis implants compared with normal endometrium has led to pilot studies using anastrozole co-administered with progestins in patients with

endometriosis resistant to conventional medical and surgical therapies (37). Efficacy has been demonstrated for relief of pelvic pain when aromatase inhibitors were combined with combination oral contraceptives, (38) or when aromatase inhibitors were given concomitantly with a GnRH agonist (39). The combination of letrozole and norethisterone acetate was more effective than norethisterone acetate alone in reducing pain and deep dyspareunia in women with rectovaginal endometriosis (40). A systematic review of the use of aromatase inhibitors for the treatment of pain associated with severe endometriosis concluded that aromatase inhibitors significantly reduced pain compared with GnRH agonists alone (41). The use of aromatase inhibitors with add-back progestin or oral contraceptives does not appear to be associated with significant bone loss after 6 months of treatment and, based on the available data, may be suitable for long-term (greater than 6 months) use (42).

References

1. Kendall A, Dowsett M, Folkerd E, Smith I. Caution: vaginal estradiol appears to be contraindicated in postmenopausal women on adjuvant aromatase inhibitors. Ann Oncol 2006; 17:584–7.
2. Biglia N, Peano E, Sgandurra P, Moggio G, Panuccio E, Migliardi M, et al. Low-dose vaginal estrogens or vaginal moisturizer in breast cancer survivors with urogenital atrophy: a preliminary study. Gynecol Endocrinol 2010;26: 404–12.
3. Management of gynecologic issues in women with breast cancer. Practice Bulletin No. 126. American College of Obstetricians and Gynecologists. Obstet Gynecol 2012;119: 666–82.
4. Howell A, Cuzick J, Baum M, Buzdar A, Dowsett M, Forbes JF, et al. Results of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial after completion of 5 years' adjuvant treatment for breast cancer. ATAC Trialists' Group. Lancet 2005;365:60–2.
5. Cuzick J, Sestak I, Baum M, Buzdar A, Howell A, Dowsett M, et al. Effect of anastrozole and tamoxifen as adjuvant treatment for early-stage breast cancer: 10-year analysis of the ATAC trial. ATAC/LATTE investigators. Lancet Oncol 2010;11:1135–41.
6. National Surgical Adjuvant Breast and Bowel Project. Protocol B-35: a clinical trial comparing anastrozole with tamoxifen in postmenopausal patients with ductal carcinoma in situ (DCIS) undergoing lumpectomy with radiation therapy. Available at: http://www.nsabp.pitt.edu/B-35.asp. Retrieved February 2, 2016.
7. National Comprehensive Cancer Network. Breast Cancer. Version 1. 2016. NCCN Clinical Practice Guidelines in Oncology. Fort Washington (PA): NCCN; 2016.
8. Burstein HJ, Temin S, Anderson H, Buchholz TA, Davidson NE, Gelmon KE, et al. Adjuvant endocrine therapy for women with hormone receptor-positive breast cancer: American Society of Clinical Oncology clinical practice guideline focused update. J Clin Oncol 2014;32:2255–69.
9. Francis PA, Regan MM, Fleming GF, Láng I, Ciruelos E, Bellet M, et al. Adjuvant ovarian suppression in premenopausal breast cancer. SOFT Investigators; International Breast Cancer Study Group. N Engl J Med 2015;372: 436–46.
10. Smith IE, Dowsett M, Yap YS, Walsh G, Lonning PE, Santen RJ, et al. Adjuvant aromatase inhibitors for early breast cancer after chemotherapy-induced amenorrhoea: caution and suggested guidelines. J Clin Oncol 2006;24: 2444–7.
11. Burstein HJ, Mayer E, Patridge AH, O'Kane H, Litsas G, Come SE, et al. Inadvertent use of aromatase inhibitors in patients with breast cancer with residual ovarian function: cases and lessons. Clin Breast Cancer 2006;7:158–61.
12. Bickenbach KA, Jaskowiak N. Aromatase inhibitors: an overview for surgeons. J Am Coll Surg 2006;203:376–89.
13. Moyer VA. Medications to decrease the risk for breast cancer in women: recommendations from the U.S. Preventive Services Task Force recommendation statement. U.S. Preventive Services Task Force. Ann Intern Med 2013;159: 698–708.
14. Le Ray I, Dell'Aniello S, Bonnetain F, Azoulay L, Suissa S. Local estrogen therapy and risk of breast cancer recurrence among hormone-treated patients: a nested case-control study. Breast Cancer Res Treat 2012;135:603–9.
15. Manson JE, Goldstein SR, Kagan R, Kaunitz AM, Liu JH, Pinkerton JV, et al. Why the product labeling for low-dose vaginal estrogen should be changed. Working Group on Women's Health and Well-Being in Menopause. Menopause 2014;21:911–6.
16. Majithia N, Atherton PJ, Lafky JM, Wagner-Johnston N, Olson J, Dakhil SR, et al. Zoledronic acid for treatment of osteopenia and osteoporosis in women with primary breast cancer undergoing adjuvant aromatase inhibitor therapy: a 5-year follow-up. Support Care Cancer 2016; 24:1219–26.
17. Osteoporosis. Practice Bulletin No. 129. American College of Obstetricians and Gynecologists. Obstet Gynecol 2012; 120:718–34.
18. Gnant M, Pfeiler G, Dubsky PC, Hubalek M, Greil R, Jakesz R, et al. Adjuvant denosumab in breast cancer (ABCSG-18): a multicentre, randomised, double-blind, placebo-controlled trial. Austrian Breast and Colorectal Cancer Study Group. Lancet 2015;386:433–43.
19. Delmas PD. Clinical potential of RANKL inhibition for the management of postmenopausal osteoporosis and other metabolic bone diseases. J Clin Densitom 2008;11:325–38.
20. Dowsett M, Forbes JF, Bradley R, Ingle J, Aihara T, Bliss J, et al. Aromatase inhibitors versus tamoxifen in early breast cancer: patient-level meta-analysis of the randomised trials. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Lancet 2015;386:1341–52.
21. Amir E, Seruga B, Niraula S, Carlsson L, Ocana A. Toxicity of adjuvant endocrine therapy in postmenopausal breast cancer patients: a systematic review and meta-analysis. J Natl Cancer Inst 2011;103:1299–309.
22. Henry NL, Skaar TC, Dantzer J, Li L, Kidwell K, Gersch C, et al. Genetic associations with toxicity-related discontinu-

ation of aromatase inhibitor therapy for breast cancer. Breast Cancer Res Treat 2013;138:807–16.

23. Fisher SA, Reid RL, Van Vugt DA, Casper RF. A randomized double-blind comparison of the effects of clomiphene citrate and the aromatase inhibitor letrozole on ovulatory function in normal women. Fertil Steril 2002;78:280–5.
24. Bedaiwy MA, Forman R, Mousa NA, Al Inany HG, Casper RF. Cost-effectiveness of aromatase inhibitor co-treatment for controlled ovarian stimulation. Hum Reprod 2006;21: 2838–44.
25. Malloch L, Rhoton-Vlasak A. An assessment of current clinical attitudes toward letrozole use in reproductive endocrinology practices. Fertil Steril 2013;100:1740–4.
26. Al-Fozan H, Al-Khadouri M, Tan SL, Tulandi T. A randomized trial of letrozole versus clomiphene citrate in women undergoing superovulation. Fertil Steril 2004;82: 1561–3.
27. Diamond MP, Legro RS, Coutifaris C, Alvero R, Robinson RD, Casson P, et al. Letrozole, gonadotropin, or clomiphene for unexplained infertility. NICHD Reproductive Medicine Network. N Engl J Med 2015;373:1230–40.
28. Casper RF. Letrozole versus clomiphene citrate: which is better for ovulation induction? Fertil Steril 2009;92:858–9.
29. Legro RS, Brzyski RG, Diamond MP, Coutifaris C, Schlaff WD, Casson P, et al. Letrozole versus clomiphene for infertility in the polycystic ovary syndrome. NICHD Reproductive Medicine Network. N Engl J Med 2014;371:119–29.
30. Kiddy DS, Hamilton-Fairley D, Bush A, Short F, Anyaoku V, Reed MJ, et al. Improvement in endocrine and ovarian function during dietary treatment of obese women with polycystic ovary syndrome. Clin Endocrinol (Oxf) 1992; 36:105–11.
31. Huber-Buchholz MM, Carey DG, Norman RJ. Restoration of reproductive potential by lifestyle modification in obese polycystic ovary syndrome: role of insulin sensitivity and luteinizing hormone. J Clin Endocrinol Metab 1999;84: 1470–4.
32. Polycystic ovary syndrome. ACOG Practice Bulletin No. 194. American College of Obstetricians and Gynecologists. Obstet Gynecol 2018;131:e157–71.
33. Mitwally MF, Casper RF. Use of an aromatase inhibitor for induction of ovulation in patients with an inadequate response to clomiphene citrate. Fertil Steril 2001;75:305–9.
34. Badawy A, Abdel Aal I, Abulatta M. Clomiphene citrate or letrozole for ovulation induction in women with polycystic ovarian syndrome: a prospective randomized trial. Fertil Steril 2009;92:849–52.
35. Quintero RB, Urban R, Lathi RB, Westphal LM, Dahan MH. A comparison of letrozole to gonadotropins for ovulation induction, in subjects who failed to conceive with clomiphene citrate. Fertil Steril 2007;88:879–85.
36. Tulandi T, Martin J, Al-Fadhli R, Kabli N, Forman R, Hitkari J, et al. Congenital malformations among 911 newborns conceived after infertility treatment with letrozole or clomiphene citrate. Fertil Steril 2006;85:1761–5.
37. Ailawadi RK, 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.
38. 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.
39. Soysal S, Soysal ME, Ozer S, Gul N, Gezgin T. 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;19:160–7.
40. Ferrero S, Camerini G, Seracchioli R, Ragni N, Venturini PL, Remorgida V. Letrozole combined with norethisterone acetate compared with norethisterone acetate alone in the treatment of pain symptoms caused by endometriosis. Hum Reprod 2009;24:3033–41.
41. Nawathe A, Patwardhan S, Yates D, Harrison GR, Khan KS. Systematic review of the effects of aromatase inhibitors on pain associated with endometriosis (published erratum appears in BJOG 2008;115:1069). BJOG 2008;115:818–22.
42. Attar E, Bulun SE. Aromatase inhibitors: the next generation of therapeutics for endometriosis? Fertil Steril 2006;85: 1307–18.

American College of Obstetricians and Gynecologists
409 12th Street, SW, PO Box 96920, Washington, DC 20090-6920

Aromatase inhibitors in gynecologic practice. ACOG Committee Opinion No. 738. American College of Obstetricians and Gynecologists. Obstet Gynecol 2018;131:e194–9.