

A Systematic Review of Systematic Reviews on the Use of Aromatase Inhibitors for the Treatment of Endometriosis: The Evidence to Date

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Abstract: Endometriosis is a chronic gynecologic condition that affects around 6–10% of reproductive age women. This clinical entity is characterized with pelvic pain, dysmenorrhea, dyspareunia, and infertility which are the most often presenting symptoms. Aromatase P450 is the key enzyme for ovarian estrogen biosynthesis and there is evidence that endometriotic lesions express aromatase and are able to synthesize their own estrogens. Aromatase inhibitors (AIs) are potent drugs that suppress the estrogen synthesis via suppression of aromatase. We performed a systematic review of systematic reviews and narrative reviews on the use of aromatase inhibitors in the medical management of endometriosis. We searched: PubMed (1950–2022), Google Scholar (2004–2022), Cochrane Library (2010–2022) and Researchgate (2010–2022). The search included the following medical subject headings (MeSH) or keywords: “Aromatase Inhibitors” AND “Endometriosis” AND “Systematic reviews” OR “Systematic review” AND “Reviews” OR “Reviews” AND “Endometriosis”. The electronic database search yielded initially 12,106 studies from the different databases. Further assessment of the studies resulted in exclusion of (n = 12,015) studies due to duplicates and irrelevance; Finally, 24 studies were selected for inclusion, 5 were Systematic reviews and 19 were Narrative reviews. The 5 systematic reviews were assessed by AMSTAR-2 criteria and were found to have low quality. Narrative reviews were assessed with SANRA criteria and were found to have high-quality aromatase inhibitors are potent drugs that can manage the endometriosis-related symptoms in cases where initial medical management has failed to show positive results. However, their use is limited by the adverse effects that are linked with menopausal symptoms. aromatase inhibitors can be administered as an alternative treatment in patients. Future studies with randomized design are required to reach safer conclusions and further investigation. These studies should define the therapeutic dose, new add-back therapy modalities. Future directions should examine the most-appropriate way of administration and the duration of therapy.

Keywords: endometriosis, aromatase inhibitors, systematic review, pelvic pain, adverse effects

Introduction

Endometriosis is a chronic gynecologic condition that affects around 6–10% of reproductive-age women. This clinical entity is characterized by pelvic pain, dysmenorrhea, dyspareunia, and infertility which are the most often presenting symptoms. The disease exhibits an estrogen-dependent growth of the endometrial glands and stroma outside the endometrial cavity.¹ Several risk factors of endometriosis have been reported, such as early menarche, short menstrual cycles, late menopause, low body mass index (BMI), nulliparity, increased consumption of alcohol, caffeine, and prolonged menstruation.²

The most common theory of the pathogenesis of endometriosis is the theory of retrograde menstruation; however, retrograde menstruation occurs in nearly all women and not all women are afflicted with this condition. Hence, it has been postulated that women with endometriosis are likely to contain underlying molecular abnormalities that promote the continuous growth of endometrial tissues outside the uterine cavity.³

Aromatase P450 is the key enzyme for ovarian estrogen biosynthesis. It catalyzes the conversion of androstenedione and testosterone produced in the ovarian theca cells to estrone and estradiol (E2) in the ovarian granulosa cells. Recently, there is evidence that demonstrates that endometriotic lesions express aromatase and can synthesize their own E2.⁴ Aromatase inhibitors (AIs) Aromatase Inhibitors were first used for the treatment of postmenopausal, estrogen receptor-positive advances.

Breast cancer: during the first decade of 2000 their use was established as alternative medical management of endometriosis-related symptoms.⁵

AIs are present in three generations, Aminoglutethimide, a first-generation inhibitor, suppressed the adrenals and resulted in many side effects, such as lethargy, skin rashes, and nausea, therefore its use was limited. Fadrozole and formestane are more selective second-generation inhibitors with fewer side effects; however, their administration is only intramuscular. Letrozole, anastrozole, and exemestane are the third generation of AIs. Letrozole and anastrozole are triazole derivatives characterized by being selective, reversible, and potent AIs. [Figure 1](#). Administered orally at doses of 1–5 mg/day, they inhibit estrogen levels by 97% to more than 99%; 11–13; meanwhile, exemestane is a steroidal irreversible AI effectively working at a dose of 25 mg/day.⁶ Mauri et al⁵ in 2006 published one of the first systematic reviews and meta-analyses in the international literature that compared several generations of aromatase inhibitors and inactivators with standard hormonal treatment in patients with advanced breast cancer. Similarly, since this review, several systematic and narrative reviews have been published which reported the importance of AIs in the treatment of endometriosis and the endometriosis-related symptoms in the clinical practice.

Aim

The current study aimed to carry out a systematic review of all available systematic review studies evaluating the use of aromatase inhibitors in the clinical management of endometriosis-related symptoms. In addition, we performed a systematic review of the narrative reviews in the international literature. A methodological quality assessment of all the selected studies was performed with the use of critical appraisal tools.

Materials and Methods

Search Strategy

We searched the following electronic databases: PubMed (1950–2022), Google Scholar (2004–2022), Cochrane Library (2010–2022), and Researchgate (2010–2022). The electronic literature search was conducted from January 2021 to September 2022. The search included the following (MeSH) medical subject headings or keywords: “Aromatase Inhibitors” AND “Endometriosis” AND “Systematic reviews” OR “Systematic review” AND “Reviews” OR “Reviews” AND “Endometriosis”. The last search was performed on 08/12/2021. The systematic review and the flowchart diagram were performed according to *PRISMA* (Preferred Reporting Items for Systematic Reviews and Meta-analyses), <http://prisma-statement.org/prismastatement/flowdiagram.aspx>.⁷

Inclusion and Exclusion Criteria

Full-text articles published in peer-reviewed journals and written in the English language were deemed eligible to be included in the review. Studies were excluded from the review if they had the following characteristics:

- Studies other than Systematic reviews and Narrative reviews.
 - Studies not written in the English language.
 - Conference abstracts and studies not providing sufficient clinical data.
 - Studies report aromatase administration in animals, in surgical specimens, and in an in vitro environment.

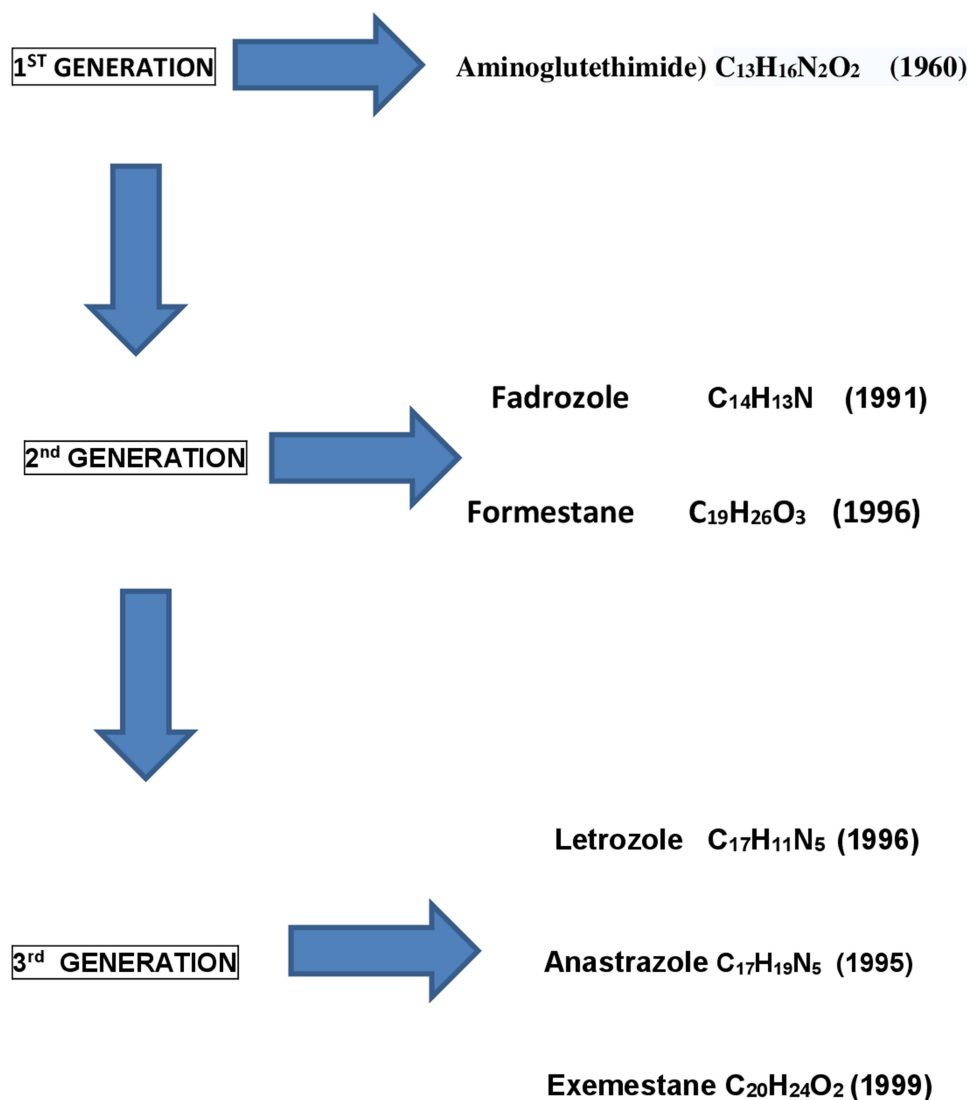


Figure 1 Exhibition of all generations of Aromatase inhibitors, chemical types and years of first distribution as therapeutic agents are demonstrated.

- Studies reporting administration of (AIs) in patients with adenomyosis.
- Studies reporting administration of (AIs) in patients with breast cancer.
- Studies reporting administration of (AIs) for assisted reproduction.
- Studies reporting administration of (AIs) in patients with myomas.
- Studies reporting administration of (AIs) in patients with gynecological cancers.

We included systematic reviews and narrative reviews that were related only to the use of aromatase inhibitors (AIs) in the management of endometriosis-related symptoms. No institutional board was required because there was an analysis of previously published clinical data.

Data Extraction

The extraction form included: the primary author; year of publication; country and city in which the study was accomplished; databases searched; flowchart methodology number of studies included; the population participants enrolled in the review; the mean age of the participants; the type of studies included in the review; the aim; the interventions and dosage of regimen reported in; the duration of treatment in months; the inclusion and exclusion

criteria; the side effects of the treatments; the pain relief; and the outcomes. All articles were obtained in full text and scrutinized for the collection of clinical data. To reduce selection bias, the abstracts and full-text papers were assessed by masking the authors as far as possible. Discrepancies between the authors were resolved through a mutual decision after discussion. Two reviewers independently appraised the articles and extracted data (PP and PT).

Quality Assessment of the Included Studies

The methodological quality of the included systematic reviews was evaluated using the AMSTAR 2 (A Measurement Tool to Assess Systematic Reviews) tool, <https://amstar.ca/Amstar-2.php>.⁸ AMSTAR 2 is a critical appraisal tool that consists of 16 items defining the quality criteria for the evaluation of the systematic reviews.⁸

The quality rating criteria are divided into four categories according to the assessment of the 16 items and are the following:

- High → Zero or one non-critical weakness: The systematic review provides an accurate and comprehensive summary of the results of the available studies that address the question of interest.
- Moderate → More than one non-critical weakness: The systematic review has more than one weakness, but no critical flaws. It may provide an accurate summary of the results of the available studies that were included in the review.
- Low → One critical flaw with or without non-critical weaknesses: The review has a critical flaw and may not provide an accurate and comprehensive summary of the available studies that address the question of interest.
- Critically low → More than one critical flaw with or without non-critical weaknesses: The review has more than one critical flaw and should not be relied on to provide an accurate and comprehensive summary of the available studies.

The methodological quality of the narrative reviews was evaluated according to SANRA (Scale for the Assessment of Narrative Review Articles) tool for assessment of narrative reviews <https://www.cognibrain.com/sanra-tool-for-assessing-narrative-review-articles/>.⁹ SANRA is a critical appraisal tool used to assess the quality of narrative reviews and research articles, it consists of a six-question questionnaire. Each question is evaluated on a scale from zero to two (ie, 0, 1, and 2) resulting in a maximum cumulative score of 12 for each review. Studies with a maximum score of five (ie, 0–5) were considered low-quality, those with a total score from five to seven (ie, 5–7) were regarded as a medium-quality, and those with a score from seven to ten (ie, 7–10) were considered as high-quality. Initial screening of titles and abstracts and exclusion of duplicate studies was performed in EndNote (Clarivate Analytics, Philadelphia, PA, USA). Rating of studies with AMSTAR-2 and SANRA tools, respectively, was performed by two reviewers independently PP and PT.

Statistical Analysis

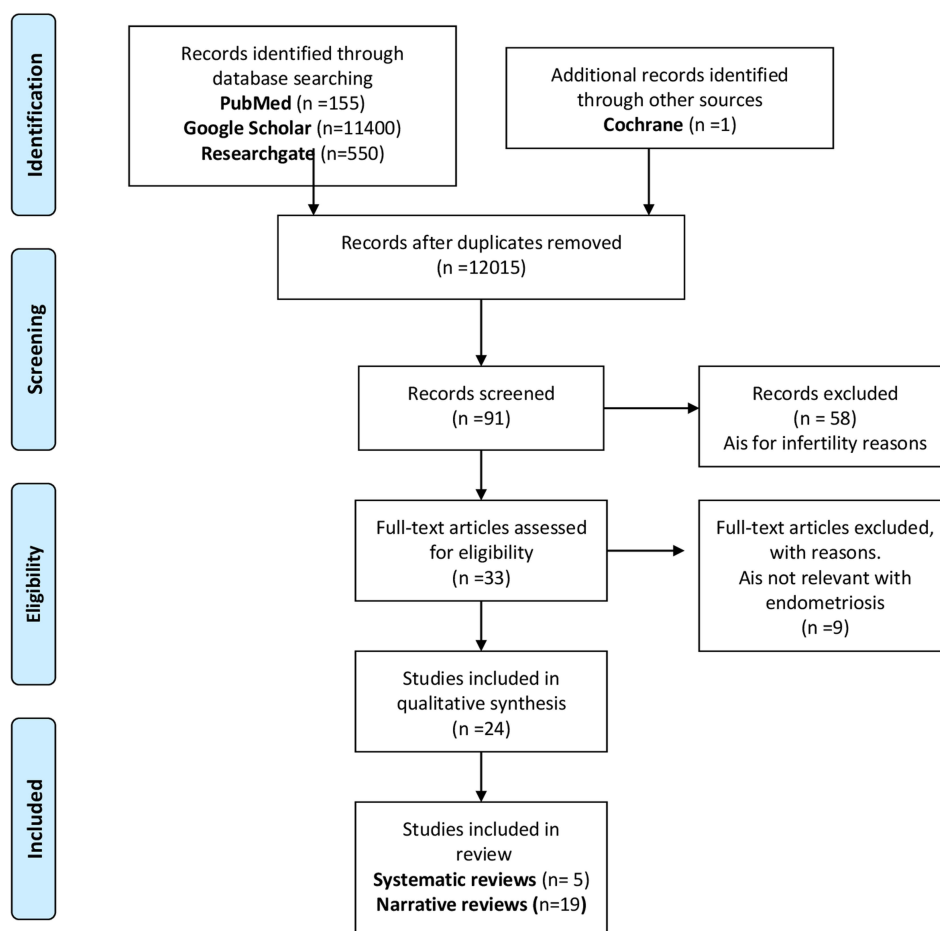
Clinical data collected from the selected studies were entered into an Excel v160 spreadsheet (Microsoft Corporation 2018). We performed descriptive statistical analyses using SPSS version 23 (IBM Corporation) and Excel version 16.0 (Microsoft Corporation, 2018). The quantity of included publications was calculated per year and per country. We calculated the mean values and standard deviation of the age of participants, time of follow-up, and time of duration of treatment as reported in the systematic reviews.

Results

The electronic database search yielded initially 12,106 studies from the following databases PubMed (n = 155), Google Scholar (n = 11,400), Researchgate (n = 500), and Cochrane (n = 1). Further assessment of the studies resulted in exclusion of 12,015 studies due to duplicates and irrelevance; 58 studies reporting AIs for reproductive reasons; 10 for non-relevant criteria (Clinical conditions other than endometriosis: Breast cancer, Adenomyosis, Myomas, Endometrial cancer). Finally, 24 studies were selected for inclusion, 5 were Systematic reviews^{10–14} and 19 were Narrative reviews.^{15–33} The PRISMA flowchart of the process of the selection of the studies is exhibited in [Figure 2](#) The systematic reviews dated from 2008 to



PRISMA 2009 Flow Diagram



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *PLoS Med* 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit www.prisma-statement.org.

Figure 2 The PRISMA flowchart of the process of the selection of the studies.

2021^{10,14} and the narrative reviews dated from 1999 to 2018.^{15,33} The majority of the studies originated from the USA (n = 9)-37.5%,^{15–17,20,22,24,25,27,28} followed by Italy (n = 7)-29.1%^{12,13,19,23,29,31,33} and Belgium (n = 2)-8.3%^{18,26} the rest of the countries UK,¹⁰ Greece,¹¹ China,¹⁴ Turkey,²¹ Egypt³⁰ Poland³² presented with one study,(n=1)-4.1%. The most frequent year of publications was 2011 with (n = 4)-16.6% studies.^{11,12,26,27} The percentage of the included publications per country and per year are exhibited in **Figure 3**. All studies were performed in university teaching settings; the total population of patients enrolled in these 5 systematic reviews was 2650 women.

Overview of Systematic Reviews

In total 5 systematic reviews were included in the study.^{10–14} The studies originated from UK,¹⁰ Greece,¹¹ Italy^{12,13} and China.¹⁴ The clinical data of the included systematic reviews are exhibited in **Table 1**.

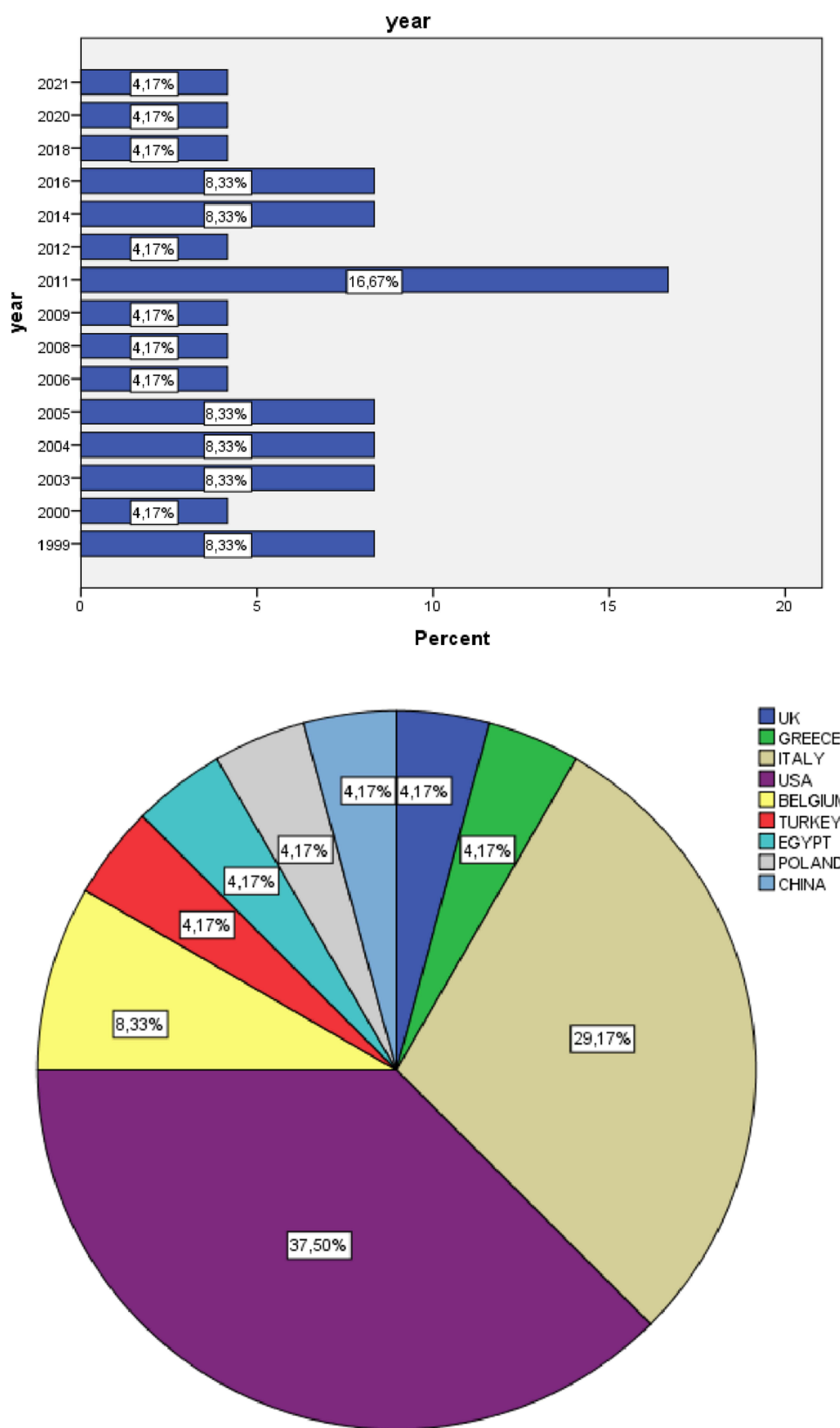


Figure 3 Histogram exhibiting the percentages of publications per year and pie-chart exhibiting the percentages of publications of the included studies per country.

Table 1 With the Data of the 5 Included Systematic Reviews

| Author Year | Country City | Databases Searched | FLOWCHART MethOdology | (N=) Studies | Population Participants | Mean Age | Type of Studies (N=) | Aim | Interventions (Type of Study and Reference) | Treatment in Months | Inclusion and Exclusion Criteria | Side Effects | Outcomes Pain Relief | Outcomes Size- Life-Quality | |
|----------------------------|---------------|--|-----------------------|--------------|-------------------------|----------|--|--|--|-------------------------------------|---|---|---|---|---|
| Nawathe 2008 ¹⁰ | UK Birmingham | MEDLINE (1950–2007) EMBASE (1974–2007) CINAHL (1982–2007) Cochrane (2007) | Yes | 8 | 137 | 31.3±4.9 | Nonrandomised (n=2) Prospective | Medical management of pelvic pain | 2.5 mg letrozole+ 1 2.5 mg NoR ³⁸ norethidrone acetate + vit D+calcium | 7.5±4.5 mts Range (3–18) mts | Women with symptoms of endometriosis previously treated medically or surgically | Reduction of BD in (n=4) studies ^{34,38,40,41} | Pain improved in (n=5) studies ^{36,38–41} | Reduction of size in (n=3) studies ^{34,38,40} | |
| | | | | | | | Nonrandomised (n=1) RCT (n=1) | | 0.25 mg anastrozole PV NoR ³⁹ + Calcium and Vit D | | | | | | Treatment with aromatase inhibitors compared with standard medical treatment |
| | | | | | | | Case reports (n=4) | | 2.5 mg letrozole +calcium CR ³⁶ and vitamin D | | | | | | Pain relief measured using analogue or numeric pain scale or quality of life scales |
| | | | | | | | 1 mg anastrozole + calcium CR ³⁴ and 10 mg aledronate | | | | | | | | |
| | | | | | | | 1 mg anastrozole + 200 mg CR ³⁵ prometrium + 12.5–30 mg rofecoxib + vitamin D | | | | | | | | |
| | | | | | | | Letrozole CR ³⁷ | | | | | | | | |
| | | | | | | | 1 mg anastrozole +0.2 PNoR ⁴⁰ micrograms ethinyl E2+0.1 mg levonorgestrel | | | | | | | | |
| | | | | | | | 3.6 mg goserelin + 1 mg RCT ⁴¹ anastrozole vs 3.6 mg goserelin | | | | | | | | |
| Polyzos 2011 ¹¹ | Larisa Greece | MEDLINE (1950–2008) | No | 5 | 5 | 54.2±4.8 | Case reports (N=5) ^{34,37,43–45} | Medical management of previous treated endometriosis in postmenopausal women | Anastrozole 1mg 1st ³⁴ | 9±5.6 mts Range (15 days-18 mts) | Women with postmenopausal endometriosis | Reduction in BD (n=1) study ³⁴ | Pain relief in (n=4) studies ^{34,37,43,44} | Reduction of size of lesions in (n=3) studies ^{34,37,44} | |
| | | | | | | | | | Letrozole 2.5 mg 2nd ³⁷ | | | | | | |
| | | | | | | | | | Exemestane 25 mg 3rd ⁴⁵ | | | | | | Hot flushes in (n=1) study ⁴⁵ |
| | | | | | | | | | Letrozole 2.5 mg 3rd ⁴⁵ | | | | | | |
| | | | | | | | | | Anastrozole 1mg 4th ⁴³ | | | | | | |
| | | | | | | | | | Letrozole 5mg 5th ⁴⁴ | | | | | | |

(Continued)

Table I (Continued).

| Author Year | Country City | Databases Searched | FLOWCHART MethOdology | (N=) Studies | Population Participants | Mean Age | Type of Studies (N=) | Aim | Interventions (Type of Study and Reference) | Treatment in Months | Inclusion and Exclusion Criteria | Side Effects | Outcomes Pain Relief | Outcomes Size- Life-Quality |
|----------------------------|--------------|--|-----------------------|--------------|-------------------------|-------------|--|-----------------------------------|---|------------------------------------|--|---|---|--|
| Ferrero 2011 ¹² | Genoa Italy | MEDLINE (1966–2009) EMBASE (1980–2009) Scopus (2004–2010) Cochrane (2009) | Yes Moose gui. | 10 | 251 | 31.5 ± 1.68 | Prospective (n=5) Non comparative RCT (n=4) Prospective (n=1) Patient preference trial | Medical management of pelvic pain | 3.6 mg goserelin + 1 mg RCT ⁴¹ anastrozole vs 3.6 mg goserelin | 5.6±1.2 mts Range (2–6) mts | Premenopausal women with primary or recurrent endometriosis previously treated medically or surgically. Patients complaining of: Dyspareunia, Dysmenorrea, chronic pelvic pain, Dyschezia | Formation of cysts in (n=12) patients ⁵⁰ Adverse effects in (n=23) patients ⁵² | Pain relief in all studies No significant changes in BD | Improvement of quality of life-however pain recurred after interruption of treatment |
| | | | | | | | | | Letrozole 2.5 mg/day or RCT ¹⁷ danazol (600 mg/day) or placebo + Calcium and vit D | | | | | |
| | | | | | | | | | Letrozole 2.5 mg/day RCT ⁴⁸ or triptorelin (3.75 mg/4 weeks) or no treatment. | | | | | |
| | | | | | | | | | Letrozole 2.5 mg/day or RCT ⁴⁹ norethisterone acetate 2.5 mg/day or triptorelin (11.25 mg 3mts) + Calcium and vit D | | | | | |
| | | | | | | | | | Studies with references ^{48–40} | | | | | |
| | | | | | | | | | Letrozole 2.5 mg/ day + Nco ⁵⁰ desogestrel 75 µg /day + Calcium and vit D | | | | | |
| | | | | | | | | | Letrozole 2.5 mg/ day + Nco ⁵¹ norethisterone acetate 2.5 mg/day + Calcium and vit D | | | | | |
| | | | | | | | | | Letrozole (2.5 mg/ day)+ PPP ⁵² norethisterone acetate 2.5 mg/day or norethisterone acetate 2.5 mg/day + Calcium and vit D | | | | | |

| | | | | | | | | | | | | | | |
|--------------------------|---------------|---|-----|----|------|--------------|--|--|--|---------------------|---|--|---|--|
| Garzon2020 ¹³ | Varese Italy | MEDLINE (1990–2020) EMBASE Cochrane Library Web of Science | No | 15 | 666 | 32±1.8 | Pilot studies (n=8) Non randomized Open label (n=3) RCT (n=4) | Overview of the efficacy and safety of Ais as monotherapy and combination | Studies with references ^{48–41,47–52} Goserelin 3.6 mg sc + PP ⁵³ anastrozole 1 mg from Day 1 to Day 69 Letrozole (2.5 mg/day) + Pp ⁵⁴ norethisterone acetate (2.5 mg/day) Letrozole (5 mg/d) +norethindrone acetate (5 mg/d) add-back therapy PP ⁵⁵ Letrozole 2.5mg/d + PP ⁵⁶ NETA 2.5mg/d + Ca 1000mg/d + vitamin D 880 NETA, or triptorelin + tibolone, or desogestrel, or sequential oral contraceptive pill Letrozole 2.5mg/d + PPP ⁸² NETA 2.5mg/d + Ca 1000mg/d + vitamin D 880 OR NETA 2.5 mg/d | 6±3.28 range (3–12) | All studies reporting administration of Ais in patients with primary or recurrent endometriosis. Case reports and series were excluded. | Pregnancy loss after IVF induction ⁵³ Ntestinal cramping ⁵⁴ | Reduction OF endometrioma volume decrease of Ca-125 Amelioration of I gastrointestinal symptoms Decrease 50% of endometrioma volume Decrease of volume of recto-vaginal nodules in 67% of patients | Not reported Improved quality of life Improved quality of life. |
| Sun 2021 ¹⁴ | Sichuan China | MEDLINE (1990–2020) Cochrane Library CNKI Wanfang VIP | Yes | 19 | 1591 | 32.75 ±32.72 | RCT (n=19) | Metanalysis on levels of outcome indicators VEGF, CA15, FSH, LH, E2 PROG, IL-6, TNF-a and total effectiveness of letrozole combined with Dydrogesterone vs letrozole alone in treatment of endometriosis | Control group- Letrozole vs ^{57–75} Experiment group - Letrozole combined with Dydrogesterone per os. | 6 mts | All RCT studies with endometriosis treated with: Letrozole +Dydrogesterone vs Letrozole alone. | NS | Total effectiveness higher in experiment group p < 0:00001 VEGF, CA125, E2, P, IL-6 and TNF-a lower in experiment group No changes in LH,FSH levels in both groups | Letrozole combined with Dydrogesterone maybe be an effective treatment of endometriosis No evidence about quality of life |

Abbreviations: Ais, Aromatase inhibitors; RCT, Randomized control trial; NoR, Non randomized; PNoR, Prospective non randomized; CR, Case report; BD, Bone density; Mts, Months; Nco, Non comparative prospective; PPP, Prospective patient preference trial; NETA, Norethisterone acetate; PP, Prospective pilot study; Sc, Subcutaneous; IVF, In vitro fertility; QOL, Quality of life; PV, Per vaginam; CNKI, China National Knowledge Infrastructure; NS, not stated.

In the first study produced by Nawathe et al¹⁰ the authors performed a systematic review retrieving information from (n = 4) databases (MEDLINE, EMBASE, CINAHL, Cochrane), and flowchart methodology was used. Quality assessment of the selected studies was reported as follows: Studies with the randomized design were considered by the authors they provide a high level of evidence; the lowest level of evidence was provided by the case reports; no tool for quality assessment of these studies was reported. Inclusion criteria were women previously treated surgically and medically for endometriosis. The authors systematically reviewed (n = 7) observational studies consisting of (n = 4) case reports,^{34–37} (n = 3) non-randomized^{38–40} and (n = 1) randomized control trial (RCT),⁴¹ enrolling in a total of 137 women. Of all these women n = 135 (98.5%) were premenopausal and n = 2 (1.5%) were postmenopausal. The mean age of the enrolled participants was 31.3±4.9 range (25–57) years. The main outcomes of the studies were: Pelvic pain, Lesion size, Quality of life (QOL), and Bone density (BD). The mean treatment duration in months was 7.5±4.5 range (3–18) months and the mean duration of follow-up in months was 8.75± 6.2 months range (6–24) months. An RCT with 97 women demonstrated that AIs in combination with GnRH analogs ameliorated pain scores (P < 0.0001) combined with significant improvement in 24 months of therapy, multidimensional scores (P < 0.0001) compared with GnRH analogs alone.⁴¹ Lesion size was assessed according to ASRM (American Society of Reproductive Medicine) score of⁴² in a non-randomized study the authors reported a reduction of lesion size after combined treatment with letrozole and norethindrone.³⁸ A significant reduction of the endometriotic lesion from 900 mm² to 90 mm² was reported after treatment with Anastrozole; this was the first report in the literature of AIs as a treatment modality in endometriosis; however, a decrease of 6.2% of the Bone Density (BD) was observed.³⁴ Quality of life was reported as improved in a non-randomized study after vaginal administration of Anastrozole in patients with rectovaginal endometriosis.³⁹

Another mini-systematic review consisted only of (n = 5) case reports and reported the administration of AIs as medical management of endometriosis in postmenopausal women which was the inclusion criteria.¹¹ Polyzos et al¹¹ did not use flowchart methodology did not report a search strategy and did not assess the quality of studies. The outcomes of the studies were: Pelvic pain, Lesion size, and Bone density (BD). The mean age of these women was 31.5±1.68 range (46–61) years; the mean duration of treatment was 9±5.6 months range (15 days-18 months). All AIs of the 3rd generation were used as a treatment regimen. The authors reported pain relief in (n = 4) studies;^{34,37,43,44} a reduction of the size of lesions in (n = 3) studies.^{34,37,44} Reduction of BD in (n = 1) study³⁴ and hot flushes in (n = 1) study.⁴⁵

Ferrero et al¹² published a systematic review in 2011. The authors searched (n = 4) databases (MEDLINE, EMBASE, Scopus, Cochrane) with the use of flowchart methodology according to MOOSE (Metanalysis of Observational studies in Epidemiology) guidelines as proposed by Stroup et al.⁴⁶ Inclusion criteria were: Premenopausal women with primary or recurrent endometriosis previously treated medically or surgically and women with dyspareunia, dysmenorrhea, pelvic pain, and dyschezia. The outcomes were: Changes in the intensity of endometriosis-related pelvic pain during treatment with AIs either alone or combined with other hormonal therapies but not combined with surgery (primary outcome). Efficacy of AIs either alone or combined with other hormonal therapies in preventing the recurrence of pain after surgery for endometriosis (secondary outcome). The review included (n = 4) randomized control studies^{41,47–49} and (n = 5) prospective non-comparative-observational studies^{38–40,50,51} and (n = 1) prospective patient preference trial.⁵² The mean age of the enrolled participants was 31.5±1.68 range (23–51) years; the mean duration of treatment was 5.6±1.2 range (2–6) months. In this study, 3 new RCTs were added.^{47–49} An RCT compared AIs or danazol for 6 months, a significant reduction in pain intensity was reported.⁴⁷ Furthermore, Alborzi et al⁴⁸ carried out an RCT that compared letrozole or triptorelin or no treatment, the authors reported that the rate of recurrence was 6.4% in the letrozole group, 5.0% in patients treated with triptorelin and 5.3% in patients receiving no treatment (not statistically significant). Ferrero et al⁴⁹ compared Letrozole or norethisterone acetate or triptorelin treatment and reported a decrease in the intensity of pelvic pain. In most studies, additional treatment with Calcium and Vit D was provided.^{47,49–51} In a study by Remorgida et al,⁵⁰ the authors administered Letrozole+Desogestrel, the authors reported that all patients (n = 12) were diagnosed with cysts and the study was discontinued. In a prospective patient preference trial,⁵² combining letrozole and norethisterone acetate or norethisterone acetate (NETA) various adverse effects (irregular bleeding, depression, weight gain, insomnia, migraine, and decrease of libido) were reported in (n = 23) patients.

In the fourth systematic review published by Garzon et al,¹³ the authors searched (n = 4) databases (MEDLINE, EMBASE, Cochrane, Web of Science), without flowchart methodology. Inclusion criteria were as follows: Patients with

endometriosis (any type of diagnosis) and underwent AIs administration with or without add-back therapy, after surgery or as exclusive therapy. The authors updated the review and added 5 new studies which were not included in the previous systematic reviews.^{14,53–56} The mean age was 32±1.8 years, the mean duration of treatment was 6±3.28 range (3–12) months.

One study reported reduction in the volume of endometriomas and reduction in the levels of Ca-125 in patients treated with goserelin 3.6 mg sc + anastrozole 1 mg before in vitro fertility procedures (IVF)¹⁴ Improvement of gastrointestinal symptoms and improvement of quality of life after treatment with Letrozole and NETA were reported in a study by Ferrero et al.⁵³

Combination of letrozole (5 mg/d) +norethindrone acetate (5 mg/d) add-back therapy (daily progestins or conjugated estrogens and progestins) resulted to a decrease of 50% in volume of endometriomas after transvaginal ultrasound assessment.⁵⁴

A combination of Letrozole 2.5mg/d + NETA 2.5mg/d + Ca 1000mg/d + vitamin D 880, NETA, or triptorelin +tibolone, or desogestrel, or sequential oral contraceptive pill led to reduction of rectovaginal nodules in 67% of patients and improvement of quality of life as reported by Ferrero et al.⁵⁵

A prospective patient preference study reported reduction of endometriomas after administration of Letrozole 2.5 mg +NETA 2.5mg or NETA 2.5 mg alone.⁵⁶

Sun et al¹⁴ performed a systematic review and meta-analysis of 19 studies published in Chinese language.^{57–75}

The meta-analysis was registered in PROSPERO website (<https://www.crd.york.ac.uk/prospéro>). The authors searched the PubMed, Cochrane Library, China National Knowledge Infrastructure (CNKI), Wanfang databases and VIP Database. Randomized control trials (RCT) were included only in the systematic review if they compared Letrozole +Dydrogesterone (experiment group) vs Letrozole alone (control group) for treatment of endometriosis; flowchart methodology was used; dosage regimen was not specified; duration of treatment was 6 months. The outcome measures were the following: Total effectiveness, Vascular Endothelial Growth Factor (VEGF) level, Carbohydrate Antigen 125 (CA125) level, Follicle-Stimulating Hormone (FSH) level, Luteinizing Hormone (LH) level, estrogen (E2) level, progesterone (P) level, interleukin-6 (IL-6) level, and tumor necrosis factor- α (TNF- α) levels. Meta-analysis exhibited that total effectiveness was significantly higher in experiment group (OR 6.21, 95% CI 4.17 to 9.24; $p < 0.00001$); levels of VEGF, CA125, E2, P, IL-6 and TNF- α were found to be lower in experiment group (Letrozole+Dydrogesterone); whilst no changes in levels of FSH and LH were observed in both groups. The authors performed risk of bias assessment with Cochrane quality assessment tool <https://methods.cochrane.org/bias/resources/rob-2-revised-cochrane-risk-bias-tool-randomized-trials>; great heterogeneity was observed between the studies in the interpretation of the results. Adverse effects of the treatment were not reported by the authors in any group.

Quality Assessment of the Systematic Reviews

The methodological quality of the included systematic reviews was evaluated with AMSTAR 2 tool⁸ which is online at https://amstar.ca/Amstar_Checklist.php. The results of the assessment are exhibited in Table 2. The analysis showed that one systematic review was of critically low-quality,³⁴ three systematic reviews^{10,35,36} were of low quality and one systematic review¹⁴ was of high quality according to the 16 items of AMSTAR 2. Four systematic reviews^{10,34–36} did not meet the criteria in item 9 which questions if the authors used a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review. In addition, all the studies did not meet the criteria in item 10 which questioned if the authors reported on the sources of funding for the studies included in the review. Four studies did not report in item 15, which asked If they performed the quantitative synthesis and if the authors carried out an adequate investigation of publication bias (small study bias) and discussed its likely impact on the results of the review. Finally, items 11 and items 12 were not applied in four systematic reviews,^{10,34–36} because it was not performed by the authors; these items addressed the question if a meta-analysis was performed with statistical methods (item 11), and if this meta-analysis which was performed included an assessment of the Risk of Bias-(RoB) (item 12). The systematic review,¹⁴ which was assessed and found to be of high quality, met the criteria of 15 items.

Table 2 Table Exhibiting the Results of Quality Assessment of the Included Systematic Reviews According to AMSTAR-2 Criteria

| Author Year | Item 1 | Item 2 | Item 3 | Item 4 | Item 5 | Item 6 | Item 7 | Item 8 | Item 9 | Item 10 | Item 11 | Item 12 | Item 13 | Item 14 | Item 15 | Item 16 | AMSTAR 2 Rating |
|----------------------------|--------|-------------|--------|--------|--------|--------|--------|--------|--------|---------|---------|---------|---------|---------|---------|---------|-----------------|
| Nawathe 2008 ¹⁰ | Yes | Partial Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | No | N/A | N/A | Yes | Yes | No | Yes | Low |
| Polyzos 2011 ³⁴ | Yes | Partial Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | No | N/A | N/A | No | No | No | Yes | Critically Low |
| Ferrero 2011 ³⁵ | Yes | Partial Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | No | N/A | N/A | Yes | Yes | No | Yes | Low |
| Garzon 2020 ³⁶ | Yes | Partial Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | No | N/A | N/A | Yes | No | No | Yes | Low |
| Sun 2021 ¹⁴ | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | Yes | Yes | Yes | Yes | Yes | Yes | High |

Abbreviation: N/A, Not applied.

Narrative Reviews and Quality Assessment

In total 19 narrative reviews were included in the systematic review. Studies were assessed with SANRA tool for assessment of narrative reviews. All studies performed a detailed and well-designed narrative review on the use of AIs as a medical treatment for endometriosis. The summary of the included narrative reviews is exhibited in Table 3. The table contains the following data: Author and year of publication; the country and city of publication; conclusions of the narrative reviews; the scores; the quality of narrative reviews. Detailed aspects and information about the biological

Table 3 Demonstration of the Narrative Reviews and Their Assessment According to SANRA (Scale for the Assessment of Narrative Review Articles)

| Author Year | Country City | Aim | Conclusions of the Narrative Review | SANRA Scores | Quality |
|----------------------------------|----------------|--|--|--------------|---------|
| Zeitoun et al 1999 ¹⁵ | USA Dallas | Describe therapeutic role of Aromatase inhibitors | Etiology of Endometriosis based on increase of E2 | 9 | High |
| Bulun et al 1999 ¹⁶ | USA Dallas | Describe therapeutic role of Aromatase inhibitors | Molecular aberrations are found in endometriotic tissue | 9 | High |
| Bulun et al 2000 ¹⁷ | USA Dallas | Describe therapeutic role of Aromatase inhibitors | Molecular aberrations are found in endometriotic tissue | 10 | High |
| D'Hooghe 2003 ¹⁸ | Belgium Leuven | Overview current and new treatments of endometriosis | Aromatase inhibitors are useful against endometriosis | 9 | High |
| Vigano et al 2003 ¹⁹ | Italy Milano | Overview current and new treatments of endometriosis | Aromatase inhibitors are useful against endometriosis | 9 | High |
| Bulun et al 2004 ²⁰ | USA Chicago | Describe therapeutic role of Aromatase inhibitors | Endometriotic tissues contain aromatase enzyme | 9 | High |
| Karaer et al 2005 ²¹ | Turkey Manisa | Describe therapeutic role of Aromatase inhibitors | Aromatase inhibitors will cure estrogen dependent diseases | 9 | High |
| Bulun et al 2005 ²² | USA Chicago | Describe therapeutic role of Aromatase inhibitors | Endometriotic tissues contain aromatase enzyme | 9 | High |
| Ferrero et al 2005 ²³ | Italy Genoa | Describe therapeutic role of Aromatase inhibitors | Aromatase inhibitors reduce pain due to endometriosis | 9 | High |
| Attar et al 2005 ²⁴ | USA Chicago | Describe therapeutic role of Aromatase inhibitors | Aromatase inhibitors reduce pain and size of lesions | 10 | High |
| Ferrero et al 2009 ²⁵ | USA Chicago | Describe therapeutic role of Aromatase inhibitors | Aromatase inhibitors reduce pain and size of lesions | 10 | High |

(Continued)

Table 3 (Continued).

| Author Year | Country City | Aim | Conclusions of the Narrative Review | SANRA Scores | Quality |
|------------------------------------|-----------------|--|--|--------------|---------|
| Collette et al 2011 ²⁶ | Belgium Louvain | Describe therapeutic role of Aromatase inhibitors | Aromatase activity not completely involved in endometriosis | 10 | High |
| Nothnick 2011 ²⁷ | USA Kansas | Describe therapeutic role of Aromatase inhibitors | Aromatase inhibitors reduce pain and size of lesions | 10 | High |
| Pavone et al 2012 ²⁸ | USA Chicago | Describe therapeutic role of Aromatase inhibitors | Aromatase inhibitors reduce pain and size of lesions | 10 | High |
| Ferrero et al 2014 ²⁹ | Italy Genoa | Describe therapeutic role of Aromatase inhibitors | Aromatase inhibitors not to be used routinely | 10 | High |
| Hashim 2014 ³⁰ | Egypt Mansoura | Describe therapeutic role of Aromatase inhibitors | Aromatase inhibitors are safe and effective in endometriosis | 11 | High |
| Benagiano et al 2016 ³¹ | Italy Rome | Overview current and new treatments of endometriosis | Aromatase inhibitors may be combined with other agents | 10 | High |
| Slopien et al 2016 ³² | Poland Poznan | Overview current and new treatments of endometriosis | Aromatase inhibitors are useful in postmenopausal endometriosis | 9 | High |
| Ferrero et al 2018 ³³ | Italy Genoa | Describe therapeutic role of Aromatase inhibitors | Aromatase inhibitors to be used in women with resistant symptoms | 10 | High |

mechanisms of suppression of endometriosis by aromatase inhibitors were provided from all reviews. All the studies were assessed and showed all high quality. Only one study³⁰ obtained the highest score of 11, this was because the authors performed and described a literature search, which is the 3rd item of all 6 items of SANRA. Nine studies obtained a score of 10, in these reviews, the authors neither performed nor described a literature search.^{17,24–29,31,33} Nine studies obtained a score of 9 this rating was because the aim of these studies was formulated in general and not in concrete questions according to the 2nd item of SANRA.^{15,16,18–23,32}

Strengths and Limitations

In the current study, we strived to perform an extensive and analytical systematic review of systematic reviews and narrative reviews. This systematic review is the first of its kind and has used a specific flowchart methodology according to PRISMA guidelines. The selected studies' systematic and narrative reviews have been assessed for their quality according to AMSTAR-2 and SANRA criteria, respectively. Low quality was observed in four of the systematic reviews; one systematic review was assessed and rated of high quality. Sun et al¹⁴ performed a systematic review and meta-analysis of 19 studies; however, these studies were written in Chinese language and accessible only to native language researchers. The authors reported that there was heterogeneity between the studies; evidence which was firstly due to sample size and measuring method and secondly due to the lack of English literature studies; which may have affected the extrapolation of results.¹⁴ High-quality assessment was observed in all narrative reviews. The fact of low quality in four of the systematic reviews was due to the lack of meta-analysis of randomized control studies and the inclusion of non-homogenous observational studies and case reports. These studies showed a greater risk of bias (RoB). About the narrative reviews, it was observed a high rating due to the agreement in most of the criteria of SANRA.

Discussion

In the current review, we observed that four systematic reviews^{10–13} were associated with low methodological quality due to lack of meta-analysis and one systematic review with high methodological quality due to performance of meta-analysis.¹⁴ Clinical data from observational studies have not been conclusive. Narrative reviews exhibited high quality; however, the level of evidence provided by these studies is significantly lower than the systematic reviews.

Aromatase inhibitors are in the first line of treatment for estrogen-receptor-positive breast cancer.⁷⁶

All the trials and reviews reported data about third-generation AIs. The most investigated aromatase inhibitor, which demonstrated effectiveness, was letrozole at the dosage of 2.5 mg/day combined with norethisterone-acetate (NETA) 2.5 mg/day for six months as reported by Garzon et al.¹³ Sun et al¹⁴ performed a meta-analysis of 19 studies comparing the administration of Letrozole+Dydrogesterone vs Letrozole alone for 6 months. The authors did not define the dosage, furthermore adverse effects were not reported; the studies were all written in Chinese language. Meta-analysis exhibited significant heterogeneity between the studies.¹⁴ A standard dose and standard regiment of treatment were not defined. Aromatase inhibitors are administered orally and can be given vaginally, a well-established route that maintains efficacy, avoids hepatic-first-pass metabolic effects, and has a better safety profile.^{13,39} Hefler et al³⁹ administered vaginally 0.25 mg Anastrozole in a 2-gr suppository as treatment of pelvic in patients with rectovaginal endometriosis with good results.

Another type of vaginal administration is the vaginal ring with silicone elastomer covered by a single continuous transparent elastomeric membrane for controlled drug release containing Anastrozole and Levonorgestrel.⁷⁷⁻⁷⁹ The first-in-human study was conducted by Schultze-Mosgau et al,⁷⁷ it was a randomized open-label, multicenter, Phase 1 study with 3 parallel groups of healthy women who received a three-dose combined Anastrozole-Levonorgestrel intravaginal ring for 56 days. Pharmacokinetics, Pharmacodynamics, and clinical safety were assessed. Further investigation of this route of administration was performed by Reinecke et al⁷⁸ a randomized, parallel-group, double-blind phase IIb clinical trial, and the authors have reached the conclusion that Anastrozole and Levonorgestrel combined in a vaginal ring do not cause functional cysts and ovulation is not inhibited.

A factor that limits the administration of AIs as a treatment option for endometriosis is the development of menopausal symptoms and adverse effects.⁴⁸ Different studies have reported that AIs decrease bone density,^{34,38,40,41} hot flashes;⁴⁵ irregular bleeding, depression, weight gain, insomnia, migraine, and decrease of libido.⁵² In all studies, patients had a bone density assessment before treatment with AIs; moreover, patients with osteopenia were excluded.¹³ In patients with decreased bone density in the premenopausal period, Calcium and Vit D should be administered simultaneously.

In addition, combination of AIs with desogestrel has resulted in the formation of cysts in all patients and the discontinuation of a trial.⁵⁰

Adverse effects due to the suppression of estrogens can be managed with combined treatment with norethisterone acetate.⁵¹ Therefore, the application of monotherapy of AIs can increase the risk of adverse effects. We should also consider the addition of add back therapy-daily small doses of progestins or conjugated estrogens with progestins given daily to reduce the effects of antiestrogenic treatment. Di Vasta et al⁸⁰ administered add back therapy in patients with endometriosis treated initially with GnRH analogs, and they reported that hormonal add-back successfully preserved bone health and improved quality of life of the randomized participants.

What is significant to be reported despite the adverse effects all studies did not report significant alterations in the hematological, cardiological, and hepatological status of the patients.¹³ This finding is of cardinal importance in minimizing the risk of subsequent mortality after AIs administration.

Dunselman et al⁸¹ in 2014 reported that the publication of only 4 randomized control trials does not support the fact that AIs can be used as first-line treatment of Endometriosis. However, it may act as an alternative treatment for endometriosis in cases where progestins, contraceptives, and GnRH (Gonadotropin releasing hormone) analogs do not provide therapeutic benefits.⁸¹ We must not forget that AIs have protective action in breast malignant and premalignant diseases, opposite progestins and contraceptives do not exhibit these actions and may increase the risk of developing premalignant and malignant breast lesions.

Conclusion

This review provides an overview of aromatase inhibitors for the treatment of endometriosis and it is the first of its kind. Analytical and extensive systematic review of previous systematic reviews and narrative reviews was performed. Endometriosis is a frequent disease that leads to socioeconomic problems, lack of cost-effectiveness in treatment. Currently, 3rd generation Aromatase inhibitors are used in clinical practice and may be used as alternative treatment in cases where first-line treatment has not been beneficial. The combination of letrozole at the dosage of 2.5 mg/day with

norethisterone-acetate (NETA) 2.5 mg/day for six months could be used in the future as treatment option. Additional studies with randomized design should be implemented in the future. These studies should define the therapeutic dose, the combination therapy which will decrease adverse effects and new add-back therapy modalities. Future directions should examine the most-appropriate way of administration and the duration of therapy.

Abbreviations

Ais, Aromatase inhibitors; RCT, Randomized control trial; NoR, Non randomized; PNoR, Prospective non randomized; CR, Case report; BD, Bone density; Mts, Months; Nco, Non comparative prospective; PPP, Prospective patient preference trial; NETA, Norethisterone acetate; PP, Prospective pilot study; Sc, Subcutaneous; IVF, In vitro fertility; QOL, Quality of life; RoB, Risk of Bias; PV, Per vaginam; GnRH, Gonadotropin releasing hormone; AMSTAR 2, A Measurement Tool to Assess Systematic Reviews; SANRA; Scale for the Assessment of Narrative Review Articles; MOOSE, Metanalysis of Observational studies in Epidemiology; ASRM, American Society of Reproductive Medicine; *PRISMA*, Preferred Reporting Items for Systematic Reviews and Meta-analyses; MeSH, medical subject headings; CINAHL, Cumulative Index to Nursing and Allied Health Literature; BMI, Body mass index; CNKI, China National Knowledge Infrastructure.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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