


ROLE OF AROMATASE INHIBITOR IN ENDOMETRIOSIS



 Cheau Ying Yoong^{1*}

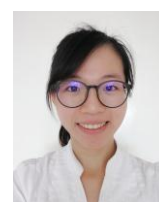
¹Newcastle University Medicine Malaysia

Email: c.y.yoong@newcastle.edu.my Tel: +60143874668

 Somsubhra De²

²Professor, Department of Obstetrics & Gynecology, Melaka Manipal Medical College, Melaka, Malaysia

Email: drsomde@gmail.com Tel: +606-2891050



(+ Corresponding author)

ABSTRACT

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Endometriosis is a chronic estrogen-dependent inflammatory disease which caused substantial impact on the quality of life in women of childbearing age and in some postmenopausal women. Surgical intervention is available but the high recurrence rate after surgery leads to extensive study on medical treatment in treating endometriosis. Currently there are various medical treatments available such as combined oral contraceptive agents, progestins and gonadotrophin-releasing hormone (GnRH) agonists. However, these medical therapies only alleviate the symptoms of endometriosis to certain extent without curing the disease. In recent years, aromatase inhibitors emerged in clinical use due to its ability to suppress aromatase which in turn reduced the production of estrogen. Several studies have been done focusing on the efficacy of aromatase inhibitor in controlling the pain symptoms and endometriosis-associated infertility. This new group of drug has also shown efficacy in symptomatic relief in postmenopausal endometriosis. Aromatase inhibitors showed comparable efficacy with other medical therapeutic modalities with a slight edge in providing both symptomatic relief and fertility treatment in endometriosis. The adverse effects of bone density might be of concern however combination with Vitamin D and calcium supplements can make the long term therapy of this drug seem possible.

Contribution/ Originality: The paper's primary contribution is finding that the aromatase inhibitor has a potential role in the management of endometriosis by providing symptomatic relief and fertility treatment. Long term use of aromatase inhibitor seems possible by combining it with calcium supplements and Vitamin D.

1. INTRODUCTION

In the olden days, women with symptoms of pelvic pain, infertility and heavy menstrual bleeding were being treated with leeches, genital mutilation and blood-letting. However, revolution of the treatment for these symptoms took place after the discovery of endometriosis, a chronic inflammatory condition with the presence of endometrial-like tissue outside the endometrial cavity. The underlying cause of endometriosis is uncertain despite many theories proposed such as retrograde menstrual regurgitation, coelomic metaplasia, immunological and genetic factors [1].

Endometriosis is influenced by cyclical hormonal changes in the body, therefore symptomatic women might experience recurrent bleeding associated with local inflammatory response. This condition is affecting about 10 percent of women and it is more prevalent in women of reproductive age due to its estrogen-dependent characteristic. Hence, hormonal treatment involves suppressing the estrogen level to induce a pseudo-menopausal

state [2]. The medical therapy in clinical use consists of combined oral contraceptive agents, progestogens and gonadotrophin-releasing hormone (GnRH) agonists. These treatments help to alleviate the symptoms, but do not cure the illness completely as endometriosis is known to be a recurrent disorder. Patients might experience recurrence of symptoms once the medical therapy is stopped.

In recent years, aromatase inhibitors have been introduced in clinical use after the discovery of aromatase pathway in ectopic endometrial tissues [3]. It was found that the endometriosis lesions expressed high levels of aromatase P450 enzyme, which is the rate-limiting enzyme in the synthesis of estrogen [4]. Hence, by inhibiting the aromatase enzyme, the level of estrogen could be suppressed. There are several studies done on aromatase inhibitor as a potential candidate drug in endometriosis treatment. This review aims to highlight the role of aromatase inhibitor in the management of endometriosis in different aspects such as endometriosis-associated pain, infertility as well as postmenopausal endometriosis and evaluate its use as long-term therapy considering the side effect profile.

2. AROMATASE IN ENDOMETRIOSIS

Aromatase is an essential enzyme in estrogen biosynthesis. In premenopausal women, high level of aromatase is found in the ovarian granulosa cell, whereas in postmenopausal women, the aromatase is mainly expressed in the adipose tissue [5]. It is not expressed in the endometrium of healthy women but increased aromatase activity is detected in the extraovarian endometriotic implants and endometriomas [6, 7].

Aromatase is a cytochrome P450 enzyme that catalyzes the conversion of androstenedione or testosterone to estrone, a less biologically active estrogen. In order to attain full estrogenic potency, estrone will be converted to estradiol by the enzyme 17-β-hydroxysteroid dehydrogenase. In the endometriotic tissue, aromatase activity is induced by prostaglandin E2 (PGE2). There is a positive feedback loop in extraovarian estrogen production because the estrogen will stimulate cyclooxygenase type-2 (COX-2) enzyme, which in turn increases the amount of PGE2 in endometriosis [8, 9]. Thus, this continuous local production of estrogen and PGE2 act as a fuel in the proliferation of endometriotic implants and favoring the inflammatory feature of endometriosis. The schematic flow is shown in Figure 1.

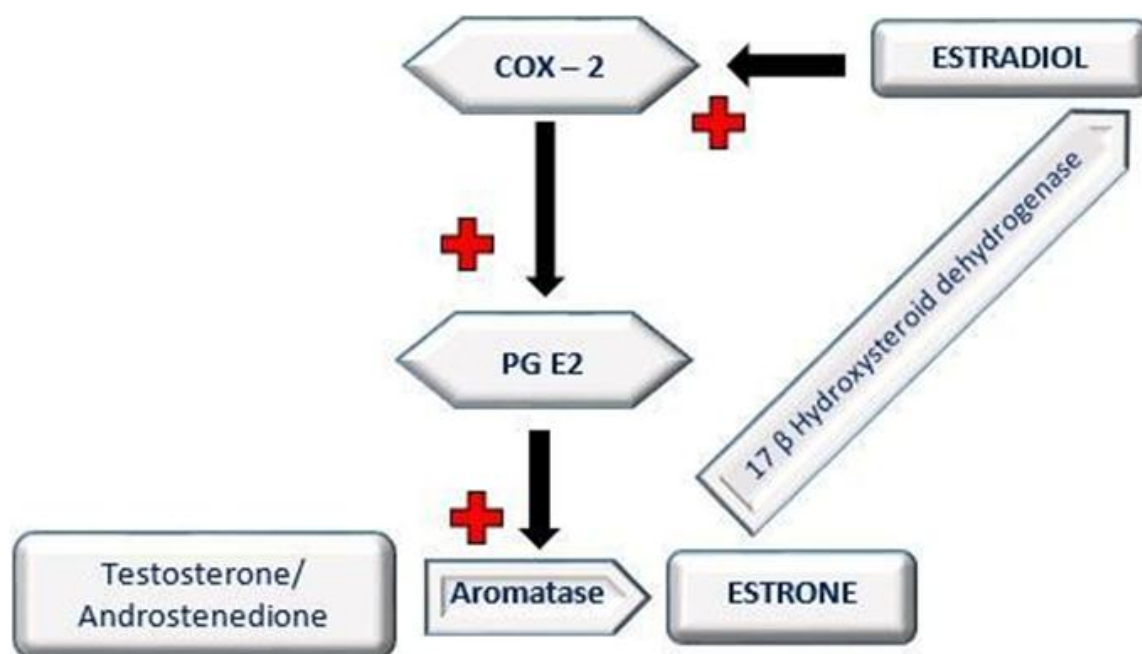


Figure-1. Positive Feedback cycle of Estradiol and Aromatase

Source: Kitawaki, et al. [8]

2.1. Aromatase Inhibitor

Aromatase inhibitor is being used in postmenopausal breast carcinoma due to its ability to suppress estrogen production by inhibiting the aromatase pathway. Currently there are three generations of aromatase inhibitor available. Each successive generation has improved specificity and better adverse effect profile. The first-generation aromatase inhibitor, Aminoglutethimide is used clinically as the second or third line treatment for advanced breast carcinoma. It is not being used in the treatment of endometriosis due to its extensive undesirable metabolic effects [9]. The second-generation of aromatase inhibitors, Fadrozole and Formestane were found to be less potent compared to the third-generation aromatase inhibitors [10, 11]. This review will focus more on the third-generation aromatase inhibitors which has the maximum potential in treating endometriosis. There are two types of third generation aromatase inhibitors, namely steroidal and non-steroidal types. Exemestane, Type I (Steroidal type), is a steroidal inhibitor that binds to the aromatase enzyme active site irreversibly. It is seldom used in clinical practice for treating endometriosis due to the poor efficacy [12].

In contrast, by interfering with the aromatase's heme group, Letrozole and Anastrozole are being classified as the third-generation type II non-steroidal aromatase inhibitors. They function by binding reversibly to aromatase which in turn competitively inhibit the conversion of androgen to estrogen [13, 14]. The effectiveness of these inhibitors depends on the concentration ratio of the competing substrate and the inhibitor. Thus, constant administration of such inhibitor is required in order to achieve a continuous inhibition of estrogen production in endometriosis.

The generations of aromatase inhibitors are shown in Table-1.

Table-1. Classification of aromatase inhibitors

Generations	Drugs	Class/Nature
First	Aminoglutethimide	Non-steroidal
Second	Fadrozole	Non-steroidal
	Formestane	Steroidal
Third	Exemestane	Type I steroidal
	Letrozole	Type II non-steroidal
	Anastrozole	Type II non-steroidal

Source: Fabian [5]

2.2. Pharmacokinetics of Anastrozole and Letrozole

Orally administered Anastrozole is absorbed from the gastrointestinal tract without being affected by food intakes. It is mainly metabolized by the isoenzymes CYP 1A2 and CYP 2C9 in the liver to an inactive metabolize triazole [15]. The half-life for 1 mg of Anastrozole is approximately 40.6 hours after oral administration. It takes 7 days for the plasma concentration to reach the steady-state level with one daily dosing [16]. Dosage adjustment in patient with renal failure is not necessary as anastrozole is eliminated mainly via the hepatic pathway [13].

Letrozole is absorbed rapidly in the gastrointestinal tract completely after oral administration. It is metabolized into an inactive carbinol metabolite by the isoenzymes CYP 3A4 and CYP 2A6 in the liver. It has plasma half-life of approximately 48 hours and achieves steady state plasma level in 60 days with daily 2.5 mg dosing [17]. However, continuous accumulation of letrozole in the body is not observed. The major elimination pathway is the renal excretion of glucuronide conjugate of the inactive carbinol. However, dose adjustment in patient with renal disease is usually not done as it is found to have no impact due to renal function [18].

2.3. Pharmacodynamics of Anastrozole and Letrozole

Both Anastrozole and Letrozole are highly selective for aromatase as there is no impairment of adrenal steroidogenesis compared to the previous two generations of aromatase inhibitors. Anastrozole is known to have higher selectivity than Letrozole. However, several studies showed that Letrozole is more potent than Anastrozole

in aromatase inhibition [18-20]. It is crucial to monitor the plasma lipid level in patients prescribed with Letrozole due to its unfavorable effect on plasma cholesterol, low density lipoprotein and apoprotein B. In the other hand, such effect is not observed in Anastrozole [13]. The usual dosage used in endometriosis is 2.5 mg of Letrozole once daily whereas for Anastrozole it is 1 mg per day.

3. AROMATASE INHIBITOR IN ENDOMETRIOSIS

3.1. Pain in Endometriosis

One of the most common symptoms experienced by patients with endometriosis is pain. The pain symptom could be described in a wide variety of combination which includes recurrent dysmenorrhea, dyspareunia, chronic abdominal pain, dyschezia and dysuria [21]. It has a significant adverse impact on the quality of life in those women with endometriosis. The exact underlying mechanism of pain in endometriosis is uncertain. It was suggested that the endometriotic tissues secrete pro-inflammatory cytokines (IL-8) which in turn increase the macrophage production and causing local inflammatory response [22, 23]. The other mechanism proposed is that there is high level of nerve growth factor (NGF) expression in the endometriotic lesions compared to normal endometrial tissues. The NGF expression is not detected in latter. Raised NGF leads to the formation of nociceptors in endometriotic implants that causes the symptom of pain in women with endometriosis. The relationship between estrogen suppression and pain relief is often debated. In ectopic endometrial tissues, augmented prostaglandin E₂ formation is stimulated by the local estrogen which in turn increases the intracellular cyclic adenosine monophosphate (cAMP) which acts as the regulator of promoter in aromatase expression. This cycle contributes to the up-regulation of estrogen production and inflammatory response. Hence, to alleviate the pain symptom, interruption of the aromatization process may be achieved through suppression of the rate-limiting enzyme by the aromatase inhibitor [24, 25]. From the aspect of NGF expression, high level of estrogen contributes to abundant nociceptors formation in the endometriotic lesions [26]. Therefore, limiting the extraovarian estrogen production by aromatase inhibitor may help in endometriosis-associated pain.

A non-randomized trial by S.Ferrero et al. suggested that pain relief was better achieved by combining Letrozole and Norethisterone acetate compared with progestin monotherapy [27]. However, the patient's compliance of the combined therapy is lower due to the higher incidence of unwanted side effects experienced by the patients such as joint pain and muscle aches. The recurrence of pain related symptoms was reported to be equal in both drug regimens, where the patients experienced pain symptoms within three months after ceasing treatment [27]. Another study reported by Abushahin et al. showed that there was improvement of pain related symptoms after six months of Letrozole treatment combining with oral contraceptive pills. However there was recurrence of pain among patients after completing the treatment regimen [28]. Another study was conducted by Amsterdam et al. to investigate the effectiveness of Anastrozole in relieving endometriosis-related pain. About 55% reduction of pain scores was achieved after completion of 1 mg Anastrozole/1 mg Levonorgestrel combination therapy for six months. However, there were no follow up data on patients' pain scores after the completion of treatment. It was found that the side effect experienced by the patients was minimal and tolerable during the period of Anastrozole administration [29].

Clinical trials of aromatase inhibitor have shown promising results in the treatment of endometriosis-related pain. However, long-term use of oral aromatase inhibitor to counteract the recurrence of pain might lead to increased risk of reduced bone density and other undesirable systematic side effects [30]. Recent studies have suggested an alternative route of administration in order to attain a better outcome with continuous use of aromatase inhibitor. Intravaginal ring which consists of Anastrozole and Levonogestrel has been brought into experimental practice and it was proposed that constant drug plasma levels can be achieved due to the continuous release of drug from the intravaginal ring. The efficacy of intravaginal drug delivery was uncertain but it was shown that by avoiding the first-pass metabolism in the liver, equivalent efficacy could be accomplished and

unwanted side effects were reduced [31, 32]. In a study done on cynomolgus monkeys using the vaginal rings, the circulating estrogen level was found to be reduced by at least 30% without leading to ovarian hyperstimulation caused by the pituitary counter regulatory pathway [33]. However, further studies have to be done to assess the safety profile and the effectiveness of vaginally administered aromatase inhibitor in various type of endometriosis. It is important to investigate if the side effect experienced by patients on aromatase inhibitor is dose dependent before concluding that intravaginal administration of aromatase inhibitor in lower dose compared to oral route could help to reduce the unwanted side effects.

3.2. Infertility in Endometriosis

The prevalence of infertility is higher in women with endometriosis. According to a survey done, 60% of women with infertility were diagnosed with endometriosis [34]. The underlying mechanism of infertility in endometriosis has been studied extensively but the direct causal relationship is still uncertain. It was suggested that the anatomical disruption caused by endometriotic lesions might lead to difficulty in conceiving. Moreover, the physiological changes from the hormonal and immunological aspects might play a role as well [35].

Clomiphene citrate (CC) has been the first-line treatment in managing subfertility for the past 50 years. It has gained popularity due to its successful ovulation rate of around 60 to 85% and a successful pregnancy rate of 30 to 40% [36, 37]. The induction of ovulation is achieved through the binding of CC to the estrogen receptors which exert an antiestrogenic effect on the hypothalamus and the anterior pituitary gland. The level of estrogen is being wrongly perceived as low by the body, leading to the removal of estrogen-negative feedback on the hypothalamus. This in turn increases the GnRH production which stimulates raised follicle stimulating hormone (FSH) and luteinizing hormone (LH) secretion from the anterior pituitary. The growth of ovarian follicles is stimulated in response to the increased FSH and ovulation occurs subsequently [38, 39]. However, the drawback of CC such as thinning of endometrial lining and ovarian hyperstimulation should not be disregarded. The discovery of aromatase inhibitor has brought a revolution to the treatment for infertility. By inhibiting the conversion of androgen to estrogen, aromatase inhibitor is able to suppress the estrogen level without depleting the estrogen receptors. Aromatase inhibitor is administered during the early phase of menstrual cycle for 5 days until the 7th day [40]. The hypothalamus will sense a low level of estrogen which in turn stimulates the anterior pituitary to produce more FSH. Ovarian follicles maturation occurs under the influence of high FSH. However, the estrogen level starts to increase upon ovulation due to the relatively short half-life of non-steroidal aromatase inhibitor which is about 45 hours compared to weeks in CC [41]. Therefore the normal central estrogen-negative feedback axis on hypothalamus remained intact and the FSH level is being suppressed. This feature is desirable as it could reduce the risk of multiple follicles release and ovarian hyperstimulation. Notably, studies have shown that aromatase inhibitor has a lower multiple pregnancy rate compared to CC and such phenomenon was observed in patients with endometriosis as well [42]. At the same time, the anti-estrogenic effect on endometrial thickness is not observed in aromatase inhibitor, making the uterus favorable for implantation to occur [43].

Other than the central mechanism of action of aromatase inhibitor, the peripheral mechanism is postulated to have a role in the treatment of infertility as well. There is accumulation of androgens in the ovary due to the inhibition of androgens to estrogen conversion. The accumulated androgens increase the follicular FSH receptor expression in the primate ovary which leads to higher sensitivity of the follicles toward the FSH stimulation [44]. Therefore, accumulation of androgens promotes folliculogenesis by augmenting the FSH effects [38].

Patients with endometriosis were found to have significantly lower fertilization and pregnancy rate [45]. Several studies have been done to investigate the potential role of aromatase inhibitor in improving fertility of patients with endometriosis. Looking at the clinical trial which has been done on patients with endometriosis, the outcome of aromatase inhibitor, Letrozole on the post-laparoscopic surgery pregnancy rate was studied. Alborzi et al. found that there was no significant difference on pregnancy rate among patients with 2 months therapy of

Letrozole, GnRH agonist (triptorelin) and without any medication. However, the formation of functional cyst was observed in up to 24.3% of patients taking Letrozole. This is significantly higher compared to triptorelin which is only 2.5% and none in patients without medication. Concern has arisen in view of the side effect and delay of conception. Therefore, postoperative medical therapy was not recommended by the authors [46].

A retrospective study on women with severe endometriosis undergoing frozen-thawed embryo transfer was conducted by Guo et al. by assessing the efficacy of Letrozole in endometrial preparation and pregnancy rate. It was found that the pregnancy rate was comparable among the use of Letrozole, hormonal replacement therapy (HRT) which consists of ethinyl estradiol and dydrogesterone as well as natural cycle. From the aspect of pregnancy complications, both Letrozole and HRT were reported with higher rate of complications compared with the natural cycle endometrial preparation. However, the success rate of pregnancy could be attained by natural cycle only when the women are having a regular menstrual cycle. Hence, the authors suggested that endometrial preparation protocols should be tailored according to individuals' conditions. The comparable efficacy of Letrozole in improving pregnancy rate should not be disregarded [47].

According to a prospective study conducted by Lossl et al., the use of Anastrozole and GnRH agonist in patients with endometrioma undergoing in-vitro fertilization (IVF) shows reduced endometriomal volume but the pregnancy rate is similar to the standard long agonist protocol. However, high pregnancy loss was noted in patients on Anastrozole and GnRH agonist therapy. Further studies should be done to investigate the effect of aromatase inhibitor on pregnancy outcome [48].

3.3. Aromatase Inhibitor in Postmenopausal Endometriosis

Endometriosis has been commonly viewed as an estrogen dependent disease that affects those women of reproductive age. However, there were cases of endometriosis being reported in postmenopausal women and raised the question of the underlying pathophysiology of postmenopausal endometriosis [49]. The prevalence of endometriosis in postmenopausal women ranges from 2% to 4% [50]. However, there are limited studies done on this particular subject and the treatment plan is complicated. Surgical approach has been proposed to be the first-line treatment in postmenopausal endometriosis in view of the potential malignancy risk of endometrial masses [51]. Some of the patients experience recurrence of symptoms after surgery which might indicate increased peripheral estrogen production in the body. Hence, alternative medical therapeutic options should be available for these patients to relieve their symptoms. Aromatase inhibitor has a potential role in postmenopausal endometriosis treatment by suppressing the external ovarian estrogen production which appears to be the main source of estrogen production in this patient group [52].

According to Polyzos et al., Anastrozole and Letrozole were found to be effective in relieving endometriosis-associated pain in postmenopausal patients. The improvement of pain symptom was observed after a 3 months period of Letrozole therapy and the pain intensity continued to regress until the patient was pain-free within 12 months of treatment [53]. In addition, Letrozole successfully alleviates the other symptoms associated with endometriosis such as bowel and urinary tract symptoms. On the other hand, Letrozole was noted to be more effective than Exemestane as there was continuance of pain symptom observed in postmenopausal woman treated with Exemestane. However, there was a solitary report of hot flushes after 4 months of the treatment with Letrozole [12].

Interestingly, in some case reports, the aromatase inhibitor illustrated the ability to shrink the endometriotic lesions in postmenopausal women. According to the case report done by Takayama et al., near-complete eradication of the endometriotic lesion was achieved after the completion of 9 months anastrozole treatment [54]. Similar finding was reported by Sasson et al., where the size of abdominal endometrioma significantly reduced after 1 month of aromatase inhibitor therapy [50]. A prospective study done on eutopic endometrial cell cultures from patients with endometriosis discovered that the use of letrozole and anastrozole showed positive result in rendering

endometriotic cell proliferation. There were significantly high levels of apoptosis observed in the cell cultures as well, suggesting the potential role of aromatase inhibitor as one of the therapeutic options in endometriosis [55].

3.4. Adverse Effects of Aromatase Inhibitors

The main mechanism of aromatase inhibitor is to create a hypoestrogenic state which is unfavorable for the endometriotic lesion. On the other hand, low level of estrogen might be associated with adverse effects such as hot flushes, myalgia, arthralgia and vaginal dryness. Hence, those symptoms should be assessed constantly to achieve a balance of endometriosis control and minimal side effects [56].

Despite all the promising results shown by aromatase inhibitor, concerns arose about reduced bone density due to the low estrogen level among postmenopausal women on aromatase inhibitor. The bone fracture rate is higher in patients receiving aromatase inhibitor as a long term therapy [57]. Therefore, co-administration of bisphosphonates, calcium and vitamin D supplements is recommended to reduce the risk of aromatase inhibitor-associated bone loss [58]. Further studies are required to ascertain the true effect of aromatase inhibitor on the bone density among premenopausal women.

Notably, Letrozole and Anastrozole are categorized under pregnancy category X. Hence its safety in premenopausal women is questioned. According to a study done on animals, exposure to aromatase inhibitor during pregnancy could have a serious impact on the fetal wellbeing. Higher risks of pregnancy loss and congenital fetal anomalies were detected. It was suggested that the interruption of aromatization pathway contributes to a hyperandrogenic environment which would affect the intrauterine embryonic growth [59]. In view of the potential teratogenicity of aromatase inhibitor reported, a retrospective study had been performed to investigate the fetal outcome of infertility treatment by Letrozole and Clomiphene citrate therapy. The rate of fetal malformation was noted to be similar in both treatment groups where the Letrozole group was reported with a congenital abnormality rate of 2.4% and the CC group with 4.8%. However, women in this study were not exposed to Letrozole during pregnancy as the half-life of it is approximately 45 hours only [60]. Therefore the direct impact of Letrozole on fetal development is uncertain. Precaution should be taken for those women on aromatase inhibitor treatment who are planning to conceive.

There are concerns that the use of aromatase inhibitor would increase the risk of cardiovascular disease. Anastrozole was found to have no significant effect on lipid profile whereas letrozole showed an undesirable effect on plasma lipid levels. The total cholesterol level for women taking Letrozole significantly increased compared to the baseline level taken 16 weeks before starting the treatment. Nevertheless, the long term clinical impact of aromatase inhibitor on cardiovascular disease is undetermined as more studies have to be done to prove the direct relationship between them [13].

3.5. Comparing Aromatase Inhibitor with Other Treatment Options

There are a few options available for the medical management of endometriosis. Norethindrone acetate is a progestin which has been approved by the U.S. Food and Drug Administration for the treatment of endometriosis [61]. Its efficacy in improving chronic pelvic pain and abnormal uterine bleeding has been proven by a few studies. The adverse effect on bone density and serum lipid profile is not reported [62]. In view of its ability to suppress ovulation and reduce the endometrial lining, it has been recommended as a long term alternative to combined oral contraceptive and laparoscopic surgery for those women with endometriosis who do not consider getting pregnant [63]. Aromatase inhibitor is found to be as effective as the Norethindrone acetate in treating endometriosis but the estrogen level is lower and the endometrial lining is thinner in women taking Letrozole [64].

Dienogest is the new member in the progestin family which has been used exponentially in treating endometriosis. It shows comparable effectiveness with Norethindrone acetate in relieving pain symptom by inhibiting ovulation, reducing PGE₂ and proinflammatory cytokines [65]. The side effect of irregular vaginal

bleeding in the beginning of therapy is minimal which improved with continuous treatment. Long term treatment of up to 52 weeks has been proven to be effective with minimal side effects [66]. This is superior compared to aromatase inhibitor considering the prolonged period of drug administration required in treating chronic symptoms of endometriosis. In spite of that, fertility issue has been one of the concerns in Dienogest use among women of childbearing age with endometriosis. Inhibition of ovulation is achieved at 2 mg daily dose of Dienogest but the ovarian activity resumed after stopping the medication for up to 6 weeks [67].

Danazol is a synthetic steroid that works by interrupting the hypothalamus-pituitary-ovary axis which in turn inhibits the LH surge in the menstrual cycle. It is very effective in symptom relief and reduction of lesion volume due to its direct androgenic impact on the endometriotic implants. However, it has limited usage considering its long-term androgenic adverse effects [68].

GnRH agonist works by inducing a state of anovulatory hypogonadotropic hypogonadism. Its effectiveness in reducing pain symptoms has been demonstrated in a few studies [69, 70]. The continual use of GnRH agonist is effective in delaying the recurrence of symptoms after laparoscopic surgery [71]. The main drawback of GnRH agonist is the high occurrence of early pain recurrence upon termination of treatment [69]. Patients with endometriosis might experience early exacerbation of symptoms due to the initial pituitary flare response. Therefore, it is recommended to administer aromatase inhibitor during the 7th to 10th day of treatment [72].

Combined oral contraceptive (COC) is commonly used as a first-line treatment for endometriosis. The efficacy of COC is proven as there are patients reported with significant improvement in pain symptom either in the rectovaginal endometriosis or bowel and bladder endometriosis [73, 74]. Most of the patients are able to tolerate the COC as a long-term therapy and it is available in different formulations. However, it is not suitable for patients desiring to conceive whereas aromatase inhibitor has a potential role in infertility treatment.

Other than the medical therapy, surgery is comparatively effective in relieving pain. There are about 30% of women with endometriosis not going through with the medical therapy due to the undesirable side effects [75]. Surgical removal of affected tissues helps to alleviate the symptoms rapidly but at the same time it is associated with risks of fistula, resection of other organs and anastomotic leakage. Recurrence of symptoms post-operatively was reported in some patients and in fact leads to the consideration of having medical treatment after surgery [76].

4. CONCLUSION

Endometriosis is a chronic inflammatory disease with estrogen dependent activity. Common symptoms experienced by patients are recurrent pelvic pain, excessive uterine bleeding, pain in urination and defecation, as well as infertility. Extensive aromatase enzymes are found in the endometriotic tissues, suggesting the conversion of androgens to estrogens which further support the growth of such tissues. By inhibiting the aromatase enzyme, the extraovarian aromatization pathway could be interrupted leading to reduced estrogen production. Hence, recent clinical trials have been done by using the third-generation aromatase inhibitor as the candidate medical therapy in treating endometriosis.

The result of aromatase inhibitor in pain relief is promising however the combination of aromatase inhibitor with other medical therapy such as progestin, COC and GnRH agonist is more recommended. Monotherapy of aromatase inhibitor is associated with higher risk of ovarian folliculogenesis which in turn leads to the formation of functional ovarian cysts. Hence, the increased production of LH and FSH could be prevented by combining the aromatase inhibitor with progestin or oral contraceptives.

The efficacy of clomiphene citrate in infertility treatment is comparable with the aromatase inhibitor based on the outcomes of successful pregnancies. The enhanced efficacy of aromatase inhibitors is mainly due to the anti-estrogenic effect on the endometrial lining as compared to CC. However, the pregnancy outcomes and teratogenicity of aromatase inhibitor requires further researches and studies.

It has effectively relieved the pain symptoms in postmenopausal women with endometriosis. However, the side effect of bone loss is a major concern especially in postmenopausal women with endometriosis. It is recommended to administer aromatase inhibitors together with bisphosphonate, calcium, and vitamin D supplements which would be a prudent approach for a long term therapy.

Lastly, further studies are required for the potential role of aromatase inhibitor in endometriotic tissue regression because of its ability to down regulate the estrogen synthesis, the fuel of endometriosis, leading to a reduction in lesion volume.

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REFERENCES

- [1] N. P. Johnson and L. Hummelshoj, "Consensus on current management of endometriosis," *Human Reproduction*, vol. 28, pp. 1552-1568, 2013. [View at Google Scholar](#)
- [2] P. Vercellini, P. Vigano, E. Somigliana, and L. Fedele, "Endometriosis: Pathogenesis and treatment," *Nature Reviews Endocrinology*, vol. 10, pp. 261-275, 2014. [View at Google Scholar](#)
- [3] S. E. Bulun, K. M. Zeitoun, K. Takayama, and H. Sasano, "Molecular basis for treating endometriosis with aromatase inhibitors," *Hum Reprod Update*, vol. 6, pp. 413-418, 2000. [View at Google Scholar](#) | [View at Publisher](#)
- [4] L. Carvalho, S. Podgaec, M. Bellodi-Privato, T. Falcone, and M. S. Abrao, "Role of eutopic endometrium in pelvic endometriosis," *Journal of Minimally Invasive Gynecology*, vol. 18, pp. 419-427, 2011. [View at Google Scholar](#) | [View at Publisher](#)
- [5] C. J. Fabian, "The what, why and how of aromatase inhibitors: Hormonal agents for treatment and prevention of breast cancer," *International Journal of Clinical Practice*, vol. 61, pp. 2051-2063, 2007. [View at Google Scholar](#) | [View at Publisher](#)
- [6] S. Ferrero, P. L. Venturini, N. Ragni, G. Camerini, and V. Remorgida, "Pharmacological treatment of endometriosis: Experience with aromatase inhibitors," *Drugs*, vol. 69, pp. 943-952, 2009. [View at Google Scholar](#) | [View at Publisher](#)
- [7] K. M. Zeitoun and S. E. Bulun, "Aromatase: A key molecule in the pathophysiology of endometriosis and a therapeutic target," *Fertility and Sterility*, vol. 72, pp. 961-969, 1999. [View at Google Scholar](#) | [View at Publisher](#)
- [8] J. Kitawaki, N. Kado, H. Ishihara, H. Koshiba, Y. Kitaoka, and H. Honjo, "Endometriosis: The pathophysiology as an estrogen-dependent disease," *Journal of Steroid Biochemistry and Molecular Biology*, vol. 83, pp. 149-155, 2002. [View at Google Scholar](#) | [View at Publisher](#)
- [9] R. J. Santen, "Recent progress in development of aromatase inhibitors," *Journal of Steroid Biochemistry and Molecular Biology*, vol. 37, pp. 1029-1035, 1990. [View at Google Scholar](#)
- [10] M. Dowsett and R. C. Coombes, "Second generation aromatase inhibitor—4-hydroxyandrostenedione," *Breast Cancer Research and Treatment*, vol. 30, pp. 81-87, 1994. [View at Google Scholar](#) | [View at Publisher](#)
- [11] L. M. Demers, "Effects of fadrozole (CGS 16949A) and letrozole (CGS 20267) on the inhibition of aromatase activity in breast cancer patients," *Breast Cancer Research and Treatment*, vol. 30, pp. 95-102, 1994. [View at Google Scholar](#) | [View at Publisher](#)
- [12] N. A. Mousa, M. A. Bedaiwy, and R. F. Casper, "Aromatase inhibitors in the treatment of severe endometriosis," *Obstetrics & Gynecology*, vol. 109, pp. 1421-1423, 2007. [View at Google Scholar](#) | [View at Publisher](#)
- [13] A. U. Buzdar, J. F. Robertson, W. Eiermann, and J. M. Nabholz, "An overview of the pharmacology and pharmacokinetics of the newer generation aromatase inhibitors anastrozole, letrozole, and exemestane," *Cancer*, vol. 95, pp. 2006-2016, 2002. [View at Google Scholar](#) | [View at Publisher](#)
- [14] B. P. Haynes, M. Dowsett, W. R. Miller, J. M. Dixon, and A. S. Bhatnagar, "The pharmacology of letrozole," *Journal of Steroid Biochemistry and Molecular Biology*, vol. 87, pp. 35-45, 2003. [View at Google Scholar](#)

- [15] S. W. Grimm and M. C. Dyroff, "Inhibition of human drug metabolizing cytochromes P450 by anastrozole, a potent and selective inhibitor of aromatase," *Drug Metabolism & Disposition*, vol. 25, pp. 598-602, 1997. [View at Google Scholar](#) |
- [16] A. D. Camp-Sorrell, "An effective, second-line hormonal treatment for advanced breast cancer," *Cancer Practice*, vol. 5, pp. 391-393, 1997. [View at Google Scholar](#)
- [17] A. Sioufi, N. Sandrenan, J. Godbillon, P. Trunet, C. Czendlik, and H. Howald, "Comparative bioavailability of letrozole under fed and fasting conditions in 12 healthy subjects after a 2.5 mg single oral administration," *Biopharmaceutics & Drug Disposition*, vol. 18, pp. 489-497, 1997. [View at Google Scholar](#) | [View at Publisher](#)
- [18] A. S. Bhatnagar, "The discovery and mechanism of action of letrozole," *Breast Cancer Research and Treatment*, vol. 105, pp. 7-17, 2007. [View at Google Scholar](#) | [View at Publisher](#)
- [19] A. S. Bhatnagar, A. M. Brodie, B. J. Long, D. B. Evans, and W. R. Miller, "Intracellular aromatase and its relevance to the pharmacological efficacy of aromatase inhibitors," *Journal of Steroid Biochemistry and Molecular Biology*, vol. 76, pp. 199-202, 2001. [View at Google Scholar](#) | [View at Publisher](#)
- [20] J. M. Dixon, L. Renshaw, O. Young, J. Murray, E. J. Macaskill, and M. McHugh, "Letrozole suppresses plasma estradiol and estrone sulphate more completely than anastrozole in postmenopausal women with breast cancer," *Journal of Clinical Oncology*, vol. 26, pp. 1671-1676, 2008. [View at Google Scholar](#) | [View at Publisher](#)
- [21] O. Triolo, A. S. Laganà, and E. Sturlese, "Chronic pelvic pain in endometriosis: An overview.," *Journal of Clinical Medicine Research*, vol. 5, pp. 153-163, 2013. [View at Google Scholar](#)
- [22] L. Giudice, "Endometriosis," *New England Journal of Medicine*, vol. 362, pp. 2389-2398, 2010. [View at Google Scholar](#)
- [23] A. Agic, H. Xu, D. Finas, C. Banz, K. Diedrich, and D. Hornung, "Is endometriosis associated with systemic subclinical inflammation?," *Gynecologic and Obstetric*, vol. 62, pp. 139-147, 2006. [View at Google Scholar](#) | [View at Publisher](#)
- [24] E. Ricciotti and G. A. FitzGerald, "Prostaglandins and inflammation," *Arteriosclerosis, Thrombosis, and Vascular Biology*, vol. 31, pp. 986-1000, 2011. [View at Google Scholar](#)
- [25] L. S. Noble, K. Takayama, K. M. Zeitoun, J. M. Putman, D. A. Johns, and M. M. Hinshelwood, "Prostaglandin E2 stimulates aromatase expression in endometriosis-derived stromal cells," *Journal of Clinical Endocrinology & Metabolism*, vol. 82, pp. 600-606, 1997. [View at Google Scholar](#) | [View at Publisher](#)
- [26] M. Morotti, K. Vincent, and C. M. Becker, "Mechanisms of pain in endometriosis," *European Journal of Obstetrics & Gynecology and Reproductive Biology*, vol. 209, pp. 8-13, 2017. [View at Google Scholar](#)
- [27] S. Ferrero, G. Camerini, R. Seracchioli, N. Ragni, P. L. Venturini, and V. Remorgida, "Letrozole combined with norethisterone acetate compared with norethisterone acetate alone in the treatment of pain symptoms caused by endometriosis," *Human Reproduction*, vol. 24, pp. 3033-3041, 2009. [View at Google Scholar](#) | [View at Publisher](#)
- [28] F. Abushahin, K. N. Goldman, E. Barbieri, M. Milad, A. Rademaker, and S. E. Bulun, "Aromatase inhibition for refractory endometriosis-related chronic pelvic pain," *Fertility and Sterility*, vol. 96, pp. 939-942, 2011. [View at Google Scholar](#) | [View at Publisher](#)
- [29] L. L. Amsterdam, W. Gentry, S. Jobanputra, M. Wolf, S. D. Rubin, and S. E. Bulun, "Anastrozole and oral contraceptives: A novel treatment for endometriosis," *Fertility and Sterility*, vol. 84, pp. 300-304, 2005. [View at Google Scholar](#)
- [30] R. Słopień and B. Męczekalski, "Aromatase inhibitors in the treatment of endometriosis," *Przegląd Menopauzalny-Menopause Review*, vol. 15, pp. 43-47, 2016. [View at Google Scholar](#) | [View at Publisher](#)
- [31] I. Reinecke, M. H. Schultze-Mosgau, R. Nave, H. Schmitz, and B. A. Ploeger, "Model-based dose selection for intravaginal ring formulations releasing anastrozole and levonorgestrel intended for the treatment of endometriosis symptoms," *Journal of Clinical Pharmacology*, vol. 57, pp. 640-651, 2017. [View at Google Scholar](#) | [View at Publisher](#)
- [32] M. H. Schultze-Mosgau, K. Waellnitz, R. Nave, S. Klein, J. Kraetzschmar, and T. Rautenberg, "Pharmacokinetics, pharmacodynamics, safety and tolerability of an intravaginal ring releasing anastrozole and levonorgestrel in healthy premenopausal women: A phase 1 randomized controlled trial," *Human Reproduction*, vol. 31, pp. 1713-1722, 2016. [View at Google Scholar](#) | [View at Publisher](#)

- [33] A. Rotgeri, H. Korolainen, O. Sundholm, H. Schmitz, U. Fuhrmann, and K. Prella, "Characterization of anastrozole effects, delivered by an intravaginal ring in cynomolgus monkeys," *Human Reproduction*, vol. 30, pp. 308-314, 2015. [View at Publisher](#)
- [34] M. Inoue, Y. Kobayashi, I. Honda, H. Awaji, and A. Fujii, "The impact of endometriosis on the reproductive outcome of infertile patients," *American Journal of Obstetrics & Gynecology*, vol. 167, pp. 278-282, 1992. [View at Google Scholar](#) | [View at Publisher](#)
- [35] S. Gupta, J. M. Goldberg, N. Aziz, E. Goldberg, N. Krajcir, and A. Agarwal, "Pathogenic mechanisms in endometriosis-associated infertility," *Fertility and Sterility*, vol. 90, pp. 247-257, 2008. [View at Google Scholar](#) | [View at Publisher](#)
- [36] E. Kousta, D. M. White, and S. Franks, "Modern use of clomiphene citrate in induction of ovulation," *Human Reproduction Update*, vol. 3, pp. 359-365, 1997. [View at Google Scholar](#) | [View at Publisher](#)
- [37] E. E. Wallach and M. G. Hammond, "Monitoring techniques for improved pregnancy rates during clomiphene ovulation induction," *Fertility and Sterility*, vol. 42, pp. 499-509, 1984. [View at Google Scholar](#) | [View at Publisher](#)
- [38] R. F. Casper and M. F. Mitwally, "Review: Aromatase inhibitors for ovulation induction," *Journal of Clinical Endocrinology & Metabolism*, vol. 91, pp. 760-771, 2006. [View at Google Scholar](#)
- [39] J. F. Kerin, J. H. Liu, G. Phillipou, and S. S. Yen, "Evidence for a hypothalamic site of action of clomiphene citrate in women," *Journal of Clinical Endocrinology & Metabolism*, vol. 61, pp. 265-268, 1985. [View at Google Scholar](#) | [View at Publisher](#)
- [40] M. F. Mitwally and R. F. Casper, "Single-dose administration of an aromatase inhibitor for ovarian stimulation," *Fertility and Sterility*, vol. 83, pp. 229-231, 2005. [View at Google Scholar](#) | [View at Publisher](#)
- [41] A. Sioufi, N. Gauduchau, V. Pineau, F. Marfil, A. Jaouen, and J. M. Cardot, "Absolute bioavailability of letrozole in healthy postmenopausal women," *Biopharmaceutics & Drug Disposition*, vol. 18, pp. 779-789, 1997. [View at Google Scholar](#) | [View at Publisher](#)
- [42] J. Toner, "Lower multiple pregnancy rates with letrozole versus clomiphene in 16,001 IUI cycles over 10 years," *Fertility and Sterility*, vol. 104, p. e326, 2015. [View at Google Scholar](#) | [View at Publisher](#)
- [43] M. F. Mitwally and R. F. Casper, "Use of an aromatase inhibitor for induction of ovulation in patients with an inadequate response to clomiphene citrate," *Fertility and Sterility*, vol. 75, pp. 305-309, 2001. [View at Google Scholar](#) | [View at Publisher](#)
- [44] K. A. Vendola, J. Zhou, O. O. Adesanya, S. J. Weil, and C. A. Bondy, "Androgens stimulate early stages of follicular growth in the primate ovary," *Journal of Clinical Investigation*, vol. 101, pp. 2622-2629, 1998. [View at Google Scholar](#) | [View at Publisher](#)
- [45] F. Azem, J. B. Lessing, E. Geva, A. Shahar, L. Lerner-Geva, and I. Yovel, "Patients with stages III and IV endometriosis have a poorer outcome of in vitro fertilization-embryo transfer than patients with tubal infertility," *Fertility and Sterility*, vol. 72, pp. 1107-1109, 1999. [View at Google Scholar](#) | [View at Publisher](#)
- [46] S. Alborzi, B. Hamed, A. Omidvar, S. Dehbashi, S. Alborzi, and M. Alborzi, "A comparison of the effect of short-term aromatase inhibitor (Letrozole) and GnRH agonist (Triptorelin) versus case control on pregnancy rate and symptom and sign recurrence after laparoscopic treatment of endometriosis," *Archives of Gynecology and Obstetrics*, vol. 284, pp. 105-110, 2011. [View at Google Scholar](#) | [View at Publisher](#)
- [47] H. Y. Guo, Y. Wang, Q. J. Chen, W. R. Chai, L. Sun, and A. Ai, "Different endometrial preparation protocols yield similar pregnancy outcomes for frozen-thawed embryo transfer in patients with advanced endometriosis," *Journal of Reproduction and Contraception*, vol. 27, pp. 1-11, 2016. [View at Google Scholar](#)
- [48] K. Lossl, A. Loft, N. L. Freiesleben, S. Bangsboll, C. Y. Andersen, and A. T. Pedersen, "Combined down-regulation by aromatase inhibitor and GnRH-agonist in IVF patients with endometriomas-a pilot study," *European Journal of Obstetrics & Gynecology and Reproductive Biology*, vol. 144, pp. 48-53, 2009. [View at Google Scholar](#) | [View at Publisher](#)
- [49] C. L. Bendon and C. M. Becker, "Potential mechanisms of postmenopausal endometriosis," *Maturitas*, vol. 72, pp. 214-219, 2012. [View at Google Scholar](#) | [View at Publisher](#)

- [50] I. E. Sasson and H. S. Taylor, "Aromatase inhibitor for treatment of a recurrent abdominal wall endometrioma in a postmenopausal woman," *Fertility and Sterility*, vol. 92, pp. 1170 e1- 1170 e4, 2009. [View at Google Scholar](#) | [View at Publisher](#)
- [51] C. Borgfeldt and E. Andolf, "Cancer risk after hospital discharge diagnosis of benign ovarian cysts and endometriosis," *Acta Obstetrica et Gynecologica Scandinavica*, vol. 83, pp. 395-400, 2004. [View at Google Scholar](#) | [View at Publisher](#)
- [52] N. P. Polyzos, H. M. Fatemi, A. Zavos, G. Grimbizis, D. Kyrou, and J. G. Velasco, "Aromatase inhibitors in postmenopausal endometriosis," *Reproductive Biology and Endocrinology*, vol. 9, p. 90, 2011 [View at Google Scholar](#) | [View at Publisher](#)
- [53] H. M. Fatemi, H. A. Al-Turki, E. G. Papanikolaou, L. Kosmas, P. De Sutter, and P. Devroey, "Successful treatment of an aggressive recurrent post-menopausal endometriosis with an aromatase inhibitor," *Reprod Biomed Online*, vol. 11, pp. 455-457, 2005. [View at Google Scholar](#) | [View at Publisher](#)
- [54] K. Takayama, K. Zeitoun, R. T. Gunby, H. Sasano, B. R. Carr, and S. E. Bulun, "Treatment of severe postmenopausal endometriosis with an aromatase inhibitor," *Fertility and Sterility*, vol. 69, pp. 709-713, 1998. [View at Google Scholar](#) | [View at Publisher](#)
- [55] G. F. Meresman, M. Bilotas, V. Abello, R. Buquet, M. Tesone, and C. Sueldo, "Effects of aromatase inhibitors on proliferation and apoptosis in eutopic endometrial cell cultures from patients with endometriosis," *Fertility and Sterility*, vol. 84, pp. 459-463, 2005. [View at Google Scholar](#) | [View at Publisher](#)
- [56] A. Elnashar, "Emerging treatment of endometriosis," *Middle East Fertility Society Journal*, vol. 20, pp. 61-69, 2015. [View at Google Scholar](#) | [View at Publisher](#)
- [57] M. Rabaglio, Z. Sun, K. N. Price, M. Castiglione-Gertsch, H. Hawle, and B. Thurlimann, "Bone fractures among postmenopausal patients with endocrine-responsive early breast cancer treated with 5 years of letrozole or tamoxifen in the BIG 1-98 trial," *Annals of Oncology*, vol. 20, pp. 1489-1498, 2009. [View at Google Scholar](#) | [View at Publisher](#)
- [58] P. Hadji, J. J. Body, M. S. Aapro, A. Brufsky, R. E. Coleman, and T. Guise, "Practical guidance for the management of aromatase inhibitor-associated bone loss," *Annals of Oncology*, vol. 19, pp. 1407-1416, 2008. [View at Google Scholar](#) | [View at Publisher](#)
- [59] G. M. Tiboni and A. Ponzano, "Fetal safety profile of aromatase inhibitors: Animal data," *Reproductive Toxicology*, vol. 66, pp. 84-92, 2016. [View at Google Scholar](#) | [View at Publisher](#)
- [60] T. Tulandi, J. Martin, R. Al-Fadhli, N. Kabli, R. Forman, and J. Hitkari, "Congenital malformations among 911 newborns conceived after infertility treatment with letrozole or clomiphene citrate," *Fertility and Sterility*, vol. 85, pp. 1761-1765, 2006. [View at Google Scholar](#) | [View at Publisher](#)
- [61] C. Tosti, A. Biscione, G. Morgante, G. Bifulco, S. Luisi, and F. Petraglia, "Hormonal therapy for endometriosis: From molecular research to bedside," *European Journal of Obstetrics & Gynecology and Reproductive Biology*, vol. 209, pp. 61-66, 2017. [View at Google Scholar](#) | [View at Publisher](#)
- [62] S. Ferrero, G. Camerini, N. Ragni, P. L. Venturini, E. Biscaldi, and V. Remorgida, "Norethisterone acetate in the treatment of colorectal endometriosis: A pilot study," *Human Reproduction*, vol. 25, pp. 94-100, 2010. [View at Google Scholar](#) | [View at Publisher](#)
- [63] P. Vercellini, G. Pietropaolo, O. De Giorgi, R. Pasin, A. Chiodini, and P. G. Crosignani, "Treatment of symptomatic rectovaginal endometriosis with an estrogen-progestogen combination versus low-dose norethindrone acetate," *Fertility and Sterility*, vol. 84, pp. 1375-1387, 2005. [View at Google Scholar](#) | [View at Publisher](#)
- [64] M. El-Shamy, A. Gibreel, E. Refai, E. Sadek, and A. Ragab, "Aromatase inhibitor letrozole versus progestin norethisterone in women with simple endometrial hyperplasia without atypia: A prospective cohort trial," *Middle East Fertility Society Journal*, vol. 17, pp. 111-115, 2012. [View at Google Scholar](#) | [View at Publisher](#)
- [65] S. Ferrero, V. Remorgida, P. L. Venturini, and N. Bizzarri, "Endometriosis: The effects of dienogest," *British Medical Journal Clinical Evidence*, 2015.
- [66] M. P. Andres, L. A. Lopes, E. C. Baracat, and S. Podgaec, "Dienogest in the treatment of endometriosis: Systematic review," *Archives of Gynecology and Obstetrics*, vol. 292, pp. 523-529, 2015. [View at Google Scholar](#) | [View at Publisher](#)

- [67] A. E. Schindler, "Dienogest in long-term treatment of endometriosis," *International Journal of Women's Health*, vol. 3, pp. 175-84, 2011. [View at Google Scholar](#) | [View at Publisher](#)
- [68] R. Godin and V. Marcoux, "Vaginally administered danazol: An overlooked option in the treatment of rectovaginal endometriosis?" *Journal of Obstetrics and Gynaecology Canada*, vol. 37, pp. 1098-1103, 2015. [View at Google Scholar](#) | [View at Publisher](#)
- [69] L. Fedele, S. Bianchi, G. Zanconato, L. Tozzi, and R. Raffaelli, "Gonadotropin-releasing hormone agonist treatment for endometriosis of the rectovaginal septum," *American Journal of Obstetrics & Gynecology*, vol. 183, pp. 1462-1467, 2000. [View at Google Scholar](#) | [View at Publisher](#)
- [70] F. W. Ling, "Randomized controlled trial of depot leuprolide in patients with chronic pelvic pain and clinically suspected endometriosis," *Pelvic Pain Study Group Obstetrics & Gynecology* vol. 93, pp. 51-58, 1999. [View at Google Scholar](#) | [View at Publisher](#)
- [71] I. Streuli, D. de Ziegler, P. Santulli, L. Marcellin, B. Borghese, and F. Batteux, "An update on the pharmacological management of endometriosis," *Expert Opinion on Pharmacotherapy*, vol. 14, pp. 291-305, 2013. [View at Google Scholar](#) | [View at Publisher](#)
- [72] M. A. Bedaiwy, N. A. Mousa, and R. F. Casper, "Aromatase inhibitors prevent the estrogen rise associated with the flare effect of gonadotropins in patients treated with GnRH agonists," *Fertility and Sterility*, vol. 91, pp. 1574-1577, 2009. [View at Google Scholar](#) | [View at Publisher](#)
- [73] T. Harada, M. Momoeda, Y. Taketani, H. Hoshiai, and N. Terakawa, "Low-dose oral contraceptive pill for dysmenorrhea associated with endometriosis: A placebo-controlled, double-blind, randomized trial," *Fertility and Sterility*, vol. 90, pp. 1583-1588, 2008. [View at Google Scholar](#) | [View at Publisher](#)
- [74] P. Vercellini, L. Trespidi, A. Colombo, N. Vendola, M. Marchini, and P. G. Crosignani, "A gonadotropin-releasing hormone agonist versus a low-dose oral contraceptive for pelvic pain associated with endometriosis," *Fertility and Sterility*, vol. 60, pp. 75-79, 1993. [View at Google Scholar](#) | [View at Publisher](#)
- [75] N. Berlanda, E. Somigliana, M. P. Frattaruolo, L. Buggio, D. Dridi, and P. Vercellini, "Surgery versus hormonal therapy for deep endometriosis: Is it a choice of the physician?" *European Journal of Obstetrics & Gynecology and Reproductive Biology*, vol. 209, pp. 67-71, 2017. [View at Google Scholar](#) | [View at Publisher](#)
- [76] C. De Cicco, R. Corona, R. Schonman, K. Mailova, A. Ussia, and P. Koninckx, "Bowel resection for deep endometriosis: A systematic review," *British Journal of Obstetrics and Gynaecology*, vol. 118, pp. 285-291, 2011. [View at Google Scholar](#) | [View at Publisher](#)

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