Medical treatment in Endometriosis

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1. Analgesics used in the treatment of endometriosis

Endometriosis is defined as the presence of endometrial glandular and stromal tissue in various locations outside of the uterus (1). Since the definitive diagnosis is made laparoscopically, the exact prevalence of endometriosis is not known yet. Although it is thought to affect 5 to 10% of women of reproductive age (2), it has been reported that this rate can reach up to 70% in women with chronic pelvic pain. (3) The clinical findings of endometriosis may vary among individuals While some patients are completely asymptomatic and are unaware of the presence of the disease, clinical symptoms such as dysmenorrhea, chronic pelvic pain, dyspareunia, dysuria, and dyschezia may be reported by some others (4, 5).

> The most common symptom is cyclic pelvic pain (dysmenorrhea) that starts a few days before and lasts a day or two after menstruation.

Because of the variable spectrum of symptoms, clinicians should suspect endometriosis even in the presence of atypical pelvic pain (2). In a large case-control study, it was seen that 25% of women with endometriosis had dysmenorrhea, 24% urinary tract symptoms, 16% pelvic pain, 11% pain in sexual intercourse, and 2% dyschezia in the last three years before their diagnosis and sought medical care for their symptoms (6). In patients with endometriosis, pelvic pain increased 13-fold, dysmenorrhea 10-fold, pain during sexual intercourse 7-fold, and dysfunctional complaints 2-fold compared with the normal population (6).

Considering the complaints related to the disease mentioned above, it is clear that endometriosis significantly affects women's quality of life and daily activities (7). Analgesics, hormonal treatments, or combinations of these treatments can be used in the medical treatment of symptomatic patients.

In the presence of suspicion of endometriosis in patients with pelvic pain; analgesic, and hormonal treatments can be recommended before a definitive diagnosis is made by laparoscopy, an invasive procedure (8). The use of empirical therapy is widespread in adolescents suffering from dysmenorrhea and pelvic pain. However, before starting empirical treatments, the cause of pain symptoms should be investigated and other possible diagnoses should be ruled out.

Non-steroidal anti-inflammatory drugs (NSAIDs) are the most commonly used first-line treatment in patients with endometriosis due to their limited side effects and easy access (9). It is believed that increased prostaglandins cause pain in patients with endometriosis. NSAIDs are analgesics that reduce prostaglandin production and relieve cramps by inhibiting cyclo-oxygenase (COX) enzymes. COX enzymes are isoenzymes, also known as prostaglandin-endoperoxide synthase (PTGS), which provide the formation of prostanoids, such as prostaglandin and thromboxane from arachidonic acid. While the COX-1 enzyme is found in most cells in the body and is involved in thromboxane synthesis, COX-2 is an enzyme whose expression increases with inflammation and which takes part in prostacyclin synthesis. Publications suggest that NSAIDs reduce the severity of pain and have no effect on ectopic the endometrial tissue (10). Attar et al. stated in their study that naproxen sodium also reduced endometrial cell proliferation depending on the dose and time (11). In two randomized controlled studies comparing NSAID and placebo treatment in endometriosis-

related pain, NSAIDs were reported to be more effective in treatment (9). In a systematic review investigating NSAIDs' role in treating primary dysmenorrhea, NSAIDs other than niflumic acid was demonstrated to be effective in relieving pain (level of evidence IA) (12). In another review, it was concluded that the selective COX-2 inhibitors rofecoxib, lumiracoxib, and etoricoxib were as effective as naproxen and more effective than the placebo in the treatment of primary dysmenorrhea (13). However, as concerns arose about the safety of these drugs, manufacturers withdrew rofecoxib from the market in many countries (evidence level IB). In a recent Cochrane review, it was shown that NSAIDs provide effective treatment in primary dysmenorrhea treatment (14). The European Society of Human Reproduction and Embryology (ESHRE) recommends using NSAIDs and other analgesics in endometriosis-related pain in the endometriosis management guideline (8). When prescribing NSAIDs to patients, side effects associated with frequent use, including inhibition of ovulation, risk of gastric ulcers, and cardiovascular disease should be discussed. In a systematic review by Zhang et al., it was found that paracetamol was equally effective as placebo in reducing pain (15). In a study comparing the use of 1000 mg paracetamol three times a day and ibuprofen or naproxen in pain prevention, no significant difference was found between all three drugs (13). In a recent randomized controlled study with a smaller number of patients, paracetamol (acetaminophen) was shown to be superior to placebo in treating primary dysmenorrhea using 1000 mg four times a day (16).

Non-steroidal anti-inflammatory drugs (NSAIDs) are the most commonly used first-line treatment in patients with endometriosis due to fewer side effects and easier access.

In conclusion, patients should be evaluated individually to treat endometriosis-related pain, and patient symptoms and expectations should be taken into account in treatment planning. Current data show that NSAIDs are effective in pain treatment. Although NSAIDs are not effective outside treating endometriosis-related pain, they do not have a known superiority to each other. However, attention should be paid to the side effects that may arise in long-term and high doses.

2. The Role of Combined Oral Contraceptives in Endometriosis

Combined oral contraceptives (COCs) are agents containing varying estrogen and progesterone ratios and are used frequently in the first-line treatment of endometriosis-associated pain. COCs are long-term, well-tolerated and relatively cost-effective medical treatments (17, 18). They can be used for contraception in patients not planning a pregnancy and reducing the risk of ovarian and endometrial cancer.

Data show that long-term use of combined oral contraceptives reduces pain associated with endometriosis (19-21). In a double-blind, randomized study in which Harada et al. compared low-dose oral contraceptives and placebo, it was stated that they were effective in the treatment of dysmenorrhea and non-cyclic pelvic pain and reduced endometrioma size (22). However, in the Cochrane review, it was concluded that there was insufficient evidence regarding the superiority of COC use to placebo, and the recommendation for use could not be generalized (23). In another study, it was suggested that only progesterone-containing agents, especially norethindrone acetate and dienogest, were superior to COCs in preventing the anatomical spread of endometriotic lesions and reducing pain symptoms associated with endometriosis (24). It has also been reported that estrogen in COC increases endometriosis risk (25, 26). The differences in estrogen-progesterone combination, dose, follow-up time,

sample size, and the variety of tools used to assess pain among studies make the study results inadequate.

It is recommended that COC preparations containing 20 mcg of Ethinyl estradiol should be used continuously throughout the cycles in current practice. While both continuous and cyclic COC regimens appear to effectively reduce pain associated with endometriosis (22, 27), two systematic reviews report that the continuous use of the COC regimen is more effective than the cyclic COC regimen in reducing pain symptoms (17, 28). In the pathogenesis of endometriosis, retrograde menstruation and ovulation may lead to endometriosis; it is also suggested that ovarian endometrioma develops from the developing follicle or corpus luteum (29). Combined oral contraceptives have effects such as suppressing ovarian function, decidualization, endometrial tissue atrophy, and reducing the conversion of arachidonic acid to prostaglandin (4). It is thought that COCs used continuously are more effective related to the mechanism above (4).

Clinicians may prefer COCs other than NSAIDs to reduce dysmenorrhea and chronic pelvic pain associated with endometriosis. In these cases, continuous use is recommended instead of cyclic COCs for effectiveness.

In studies conducted to prevent symptoms and lesion recurrence after surgery for endometriosis, it has been concluded that long-term continuous use of COCs effectively prevents both symptoms (especially dysmenorrhea) and lesion recurrence (30). Dysmenorrhea, chronic pelvic pain and dyspareunia have been described as symptoms associated with postoperative recurrence. Short-term (6 months) cyclic or continuous use of COCs has been shown to fail to prevent recurrence (31). On the contrary, it has been reported that postoperative COC use for 24 months or more was successful in preventing both

dysmenorrhea and chronic pelvic pain and lesion recurrence, and the effect appeared faster in the group using continuous COCs compared to the group using cyclic COCs (21). Another study stated that the use of monophasic COCs for more than 24 months postoperatively decreased the VAS score significantly. This effect was more effective in continuous use than cyclic use (32, 33). Similarly, COCs used to prevent postoperative symptom recurrence were more effective than the intrauterine device with levonorgestrel. Still, it was reported that patient satisfaction was higher when using a levonorgestrel-containing intrauterine device (34). Interestingly, a study comparing continuous COC, cyclic COC, and placebo in preventing postoperative dyspareunia in another study with a 6-month follow-up period concluded that placebo was more effective than hormonal therapies. However, it has been suggested that psychosocial status can also cause dyspareunia (35).

It was concluded that the use of COCs for 2 years or more postoperatively effectively prevented endometrioma recurrence. Still, this effect disappeared after discontinuation of COC use, and recurrence increased, especially in irregular use of COCs (31). Although there are studies where no significant difference was found when using cyclic or continuous COCs in postoperative lesion recurrence, there are also studies showing that continuous use is superior (21, 33). Similarly, the use of COCs following the GnRH analog in the prevention of lesion recurrence was found to be more effective than the use of the GnRH analog alone (36). As a result, COCs seem to be effective treatments for treating endometriosis-related symptoms and the prevention of postoperative recurrences. In particular, it is thought that continuously used COCs regimens are more effective than cyclic POPs use.

Long-term use of COCs is recommended to prevent both symptom and lesion recurrence after conservative surgery for endometriosis. Continuous use is preferred to increase efficiency.

3.Progestins in Endometriosis

Medical treatments used in managing endometriosis symptoms aim to relieve pain by providing amenorrhea and function as symptomatic/suppressor rather than curative (37). As its chronic nature, the disease may require long-term medical treatment. Therefore, the ideal hormonal treatments can be used in the long term, should be well tolerated, cost-effective, and should not have a risk for the patient. No medical option is superior to another in relieving or eliminating pain (38). They are effective in up to two-thirds of women (39). Symptoms return when treatment is interrupted most of the time (37). Their usage should be individualized considering the untoward effect profile, estimated duration of treatment, age, desire for pregnancy, route of usage, sexual function, quality of life and cost (38). There are many opinions available about first-line medical treatment in the current literature (40). First-line hormonal therapies in endometriosis-related pain; estrogen/progestin combined oral contraceptives and only progesterone-containing drugs (41). Second and third-line preparations comprise GnRH agonist (± add-back therapy), aromatase inhibitors, progestin-containing intrauterine systems, androgen derivatives (e.g., danazol), and other estrogen-progestin formulations (vaginal ring and transdermal patch) (37,42).

Many randomized-controlled studies have proved that progestins to be effective in endometriosis-associated pain (43-45). It is a good choice in patients with certain or relative contraindications to estrogen hormone (history of deep vein thrombosis, smokers older than 35 years, history of cardiovascular disease, coagulation factor abnormalities, migraine, sickle cell anemia, etc.) (46).

The effects of progestins occur by various mechanisms;

a) Suppression in ovarian steroids by reducing FSH and LH secretion (47): Anovulation and amenorrhea are induced, and a relatively hypoestrogenic environment is generated. In general, treatment with progestins has enough endogenous estrogen to maintain bone density (43).

b) Anti-inflammatory and anti-angiogenic activity (43): Progesterone-mediated cell proliferation and inhibition of the production of inflammatory cytokines (48). Reducing oxidative stress (49).

c) Decreased in metalloproteinase level: Minimize endometriotic implant invasion (43).

d) Decreased aromatase activity (48).

e) Reduction of 17-beta hydroxysteroid dehydrogenase (HSD) enzyme activation and expression (48).

d) Inhibition of estrogen-induced mitosis and changes in estrogen receptors (48, 50).

Progestins have been proven by many randomized-controlled studies to be effective in the treatment of endometriosis-associated pain.

Progestins that can be used / investigated in the treatment of endometriosis;

3.1. Micronized progesterone

There is no evidence for the usage of micronized progesterone in the treatment of endometriosis. A pilot study in which micronized progesterone was used in rat endometriosis model concluded that the preparation was not effective on the regression of endometriotic implants (51). Its biggest advantage is that it is suitable for patients with

metabolic syndrome since it does not have negative metabolic effects (on the vascular system, lipid and carbohydrate metabolism, and coagulation factors) (52).

3.2. Dydrogesterone

It is old-generation progesterone that is a retro-isomer of natural progesterone. It is assumed clinically that it has no estrogenic, androgenic, glucocorticoid, and mineralocorticoid activity. It is structurally and pharmacologically similar to endogenous progesterone. It does not inhibit ovulation, and regular menstruation can be observed in its cycle use (53, 54). In previous studies, 10-60 mg continuously or cyclically between 5-25 days of menstruation use of the medications has been reported. It could be used in patients with metabolic syndrome (52).

3.3. Norethindrone acetate (NETA)

Also known as norethisterone acetate (NETA) is an orally active 19-nortesterone derivative. It has weak estrogenic and androgenic activity (38). It is partially (0.4-1%) converted to ethinylestradiol in the liver. This estrogenic effect strengthens the progestogenic effect of NETA and causes a positive effect on calcium and bone metabolism (49). NETA has a strong effect on the endometrium, and its progestogenic activity has been classified as 'strong.' Metabolically, it reduces HDL level with minimal change in lipoprotein-cholesterol distribution (55, 56). It is one of the two most researched hormones together with dienogest in the treatment of endometriosis. It has been proven to be effective in dyspareunia, dysmenorrhea, chronic pelvic pain and dyschezia (50). The FDA approves it as 5 mg/day for continuous use in endometriosis. It has been administered at a reduced dose of 2.5 mg/day in many studies, and it is effective at these doses, with fewer side effects and better tolerability (47,50,55). The most common side effect associated with NETA is weight gain (49). One

study reported 25% of breakthrough bleeding due to NETA (47). NETA can also reduce pain scores in adolescents and young patients (49). As compared with Dionegest, it is as effective as dienogest in endometriosis-related pain, sexual dysfunction, and quality of life (55).

3.4. Dienogest

It is not approved for use alone by the FDA in the treatment of endometriosis. It has been approved for use alone in Europe, Japan, Australia, and Singapore (57, 58). The standard dose in the treatment of endometriosis is 2mg per day, and it can only be used orally (37). It is one of the two most researched progestins along with NETA in the treatment of endometriosis. 19-nortestesterone derivative is a 4th generation progesterone molecule. Unlike other nortesterone derivatives (desogestrel, gestodene, norgestimate-negligible androgenic effect), it is antiandrogenic. Moreover, it lacks estrogenic, mineralocorticoid, and glucocorticoid properties (59). Like other new progesterone, it is rapidly absorbed and dispersed throughout the body (reaching maximum serum level within 1-4 hours). The low progesterone receptor activity is explained by the strong progestogenic effect of the drug on the endometrium and cervical mucus (59). The ovulation inhibition effect is relatively low, and its effect on contraception has not been adequately evaluated (59). Therefore, it is recommended to be used together with non-hormonal contraceptive methods such as additional barrier methods for contraceptives (37). Estrogen (E2) does not suppress the plasma level completely (37).

The effects on bone density are controversial. As a result of 1-year use of 2 mg/day dienogest, it was found that the density of lumbar bones in 20-75% of the study population decreased by 0.5-2.7% (58). In addition, in the adolescent group, 52 weeks of treatment with 2 mg/day dienogest was associated with decreased bone density, although it relieved

endometriosis-related symptoms (58). On the other hand, there are studies available showing that it does not affect bone density after 24 weeks of treatment (60). It has no significant or minimal effect on carbohydrate and lipid metabolism (61).

Studies have shown that its reliability, efficacy and tolerability in long-term use are clinically sufficient (62). It is effective in endometriosis-related pain symptoms such as dysmenorrhea, dyspareunia, chronic pelvic pain, endometrioma size, postoperative endometrioma recurrence pain recurrence (63). It has been shown to reduce the pain symptoms caused by rectovaginal endometriosis. Besides, it has been emphasized that it increases the quality of life and sexual functions (45). As compared with GnRH agonists, it is equally effective and has a better tolerability profile (44). Extended use of the 2 mg/day dose up to 65 weeks has a safe profile (58). The most common complaint leading to treatment discontinuation is irregular bleeding --metrorrhagia- and it has been shown that this can be reduced by prolonging the treatment period (61). No specific pregnancy-related risk or reproductive toxicity has been identified, and there is no information available on whether there is a harmful effect on pregnancy. Its use in pregnancy is not recommended (61).

3.5. Depot Medroxyprogesterone acetate

It is an effective contraception method which is 17 OH-progesterone derivative in depot form. It is administered intramuscularly (DMPA-IM) or subcutaneously (DMPA-SC) every three months (49). The new subcutaneous form (DMPA-SC) (104 mg / 0.65 ml) contains approximately 30% less dose amount than the intramuscular form (DMPA-IM) (150 mg / ml) and has different excipients (64). The curative effects of both administration routes on endometriosis symptoms have been proven by prospective randomized studies (64). The new form is associated with fewer side effects and better tolerability than the older form (46).

The most common side effects; intermenstrual bleeding, nausea, hot flushes, breast tenderness and headache (46). Bone density drops 5% below baseline between the first 2–4 years of treatment (46). In one review, it was stated that DMPA-IM might temporarily reduce bone density during the period of use. However, bone density returns completely after treatment, and there is no need to limit treatment even in the adolescent group (65). Drug-related breakthrough bleeding can negatively affect the quality of life (39).

3.6. Cyproterone acetate

It is basically a 17-hydroxyprogesterone derivative progestin with anti-androgenic properties. The dose of 12mg/day used continuously for 6 months decreased dysmenorrhea, deep dyspareunia, and non-menstrual pelvic pain and resulted in a significant improvement in the quality of life and psychiatric profile (66).

3.7. Levonorgestrel-releasing intrauterine device

This system, which secretes 20 mcg levonorgestrel daily, does not inhibit ovulation, provides atrophy and pseudo-decidualization in endometrial tissue and causes amenorrhea. Its advantages consist of avoiding repetitive applications, increased compatibility with long-term use and reduced side effect profile. In the first 3 months, bleeding irregularities, spotting, and menorrhagia are common (67). The use of 52 mg LNG-IUS in endometriosis has been proven to reduce pain effectively, and it has been stated that it can be at least as effective as GnRH analogs (68). It has been shown that LNG-IUS has similar pain scores with dienogest, but the level of patient compliance is better (69).

3.8. Desogestrel

It is the precursor molecule. After oral intake, it is converted into the active metabolite etonogestrel. It is taken orally and continuously at 75 mcg/day (49). The curative effect of the

contraceptive drug-containing Desogestrel on pain associated with endometriosis has been proven (69).

3.9. Subdermal implant containing etonogestrel

It contains 68 mg etonogestrel (ENG). It is an effective long-term contraceptive method (3-5 years). Its use in endometriosis is associated with a significant reduction in pain, increased quality of life, and increased sexual functions (49).

In conclusion, all synthetic progestins are thought to lead to an effective improvement in endometriosis symptoms by antimitotic activity and endometrial growth inhibition, and ultimately to decidualization and atrophy in endometrial lesions.

4. Gonadotropin-Releasing Hormone Analogs in Endometriosis

Medical treatment of endometriosis aims to suppress hormonally active endometriotic tissue and control pain. For these purposes, various therapeutic options have been developed and used successfully. One of these options is gonadotropin-releasing hormone analogs.

4.1.Gonadotropin-releasing hormone agonists

Gonadotropin-releasing hormone agonists (GnRH-a) are formed due to the degradation of one or more amino acids of endogenous GnRH by the endopeptidase enzyme. As a result, their half-lives increase, and they stay attached to the receptors for a longer time (70). Gonadotropin-releasing hormone agonists cause a decrease in gonadotropin (both luteinizing hormone (LH) and follicle-stimulating hormone (FSH)) secretion after their exacerbating effect, and as a result; they suppress follicular growth and ovulation and cause a decrease in circulating estradiol and progesterone. Consequently, the long-term hypoestrogenic condition causes regression of the endometriotic lesions (71).

Gonadotropin-releasing hormone agonists are the next option for women who have failed initial treatment with oral contraceptives for pain symptoms or cannot use oral contraceptives due to medical history. The literature has shown that gonadotropin-releasing hormone agonists cause a significant reduction in pelvic pain in women with endometriosis. However, it has been reminded that secondary side effects of hypoestrogenism such as bone loss, lipid profile deterioration, vaginal atrophy and dryness, and hot flashes may occur in use for more than six months (72). Therefore, it has been stated that the application of add-back therapy will provide symptomatic relief and reduce the rate of bone loss. The only FDA (Food and Drug Administration) approved agent for add-back therapy is norethindrone acetate, a progestin. However, low-dose estrogen and a combination of estrogen and progesterone are also used (73).

Gonadotropin-releasing hormone agonists are used to reducing the pain symptoms in endometriosis and reduce postoperative recurrence and reduce the effects of endometriosis in patients who will receive assisted reproductive technologies (74, 75). Studies have emphasized that GnRH-a treatment should be applied for at least 6 months in the postoperative period (74). According to randomized control studies, the application of the GnRH-a ultra-long protocol may increase the clinical pregnancy rate in patients who will undergo assisted reproductive technologies and with stage III-IV endometriosis (75).

Gonadotropin-releasing hormone antagonists

Compared with gonadotropin-releasing hormone agonists, GnRH antagonists have equivalent symptomatic improvement, with no exacerbation effect, a lower degree of hypoestrogenism, and a better side effect profile (76). Because of that, these agents have been

used in recent years for the pain symptoms of endometriosis. Another advantage of GnRH antagonists is that they can be used orally (77).

In the treatment of endometriosis, GnRH analogs can be used as an alternative treatment, especially in patients who cannot use COCs. While GnRH agonist treatments are effective for at least 6 months of use, possible side effects can be reduced with add-back treatments.

5. Aromatase inhibitors and Danazol use in endometriosis

Aromatase inhibitors (AIs) and Danazol can be used as an alternative to progesterone, COCs, and GnRH analogs of endometriosis-induced pain (78). After treatment with progesterone, COCs, and GnRH analogs medication, 30-50% of patients reported reduced pain (78). However, 5% to 25% of patients discontinued treatment due to drug side effects (79), which have brought new treatment strategies. Therefore, AIs and Danazol were considered alternative treatment options (80).

5.1 Aromatase inhibitors

The main mechanism of AI is to inhibit cytochrome P450, which catalyzes the conversion of androgens into ovaries and adrenal glands to estrogen (81). These agents inhibit estrogen production in the ovaries, brain, and peripheral adipose tissue. Besides, those regulate the local formation of estrogen in endometriotic lesions (82). The estrogen production in peripheral endometrial tissues involves the aromatization of circulating androstenedione from the adrenal to the estrone (83). This mechanism explains the clinics in patients who do not respond to the suppression of ovarian function.

The estrogen receptors consist of two receptors, the alpha estrogen receptors (ER-α) and beta receptors (ER-β), containing 55% of homologous units. ER-α is found in the ectopic endometrium and regulates regeneration and proliferation in the proliferative phase of the menstrual cycle. It also allows the proliferation of endometrial cells and their response to

progesterone (84). On the other hand, the ectopic endometrium has ER-α similar to or lower than the ectopic endometrium, while the ER-β is higher. ER-β dysregulation and hyperactivation of emergencies allow the cell to escape from the immune system and live longer (85). The ER-β signal can induce the invasion and progression of implants by regulating regeneration and proliferation in the proliferative phase of the menstrual cycle (86).

The function of ovarian aromatase activation of the peripheral tissues of aromatase within endometriotic foci (87). Polymerase chain reaction (PCR) and immunohistochemical studies have reported that patients have aromatase activities in the euphoric endometrium and ectopic endometrium. Still, aromatase activities compromise the ectopic endometrium of healthy women (87, 88). The presence of aromatase in endometriotic implants may explain the ratio of higher estradiol concentrations in endometriotic tissue, peritoneal fluid and endometrioma (89, 90). Furthermore, estrogen induces the expression of the COX-2, which raises prostaglandin E2 levels and stimulates aromatase activity by inducing the SF-1 nuclear receptor (91). For these reasons, AIs are intended to be used for endometriosis treatment by suppressing estrogen production in ovaries, peripheral tissues, and endometriotic implants.

AIs used orally have a similar efficacy despite having a different molecular structure and pharmacological properties (92). The first-generation of AIs, Aminoglutetemide, and Megestrol acetate, found in 1973, aromatase enzyme inhibitor activity 90%. 2nd generation aromatase enzyme inhibitors are Formestane, and Fadrozol has reached 92% efficiency. Finally, the third generation of AIs, Anastrozole, Letrozole, and Exemestane, inhibits the enzyme aromatase with an efficiency > 95% (92). Exemestane (Aromasin 25 mg/30 tablets) competes directly with androgens by the active part of the enzyme aromatase, covalently

binding to the enzyme and causing irreversible inactivation. Especially in the postmenopausal period, estrogen receptor-positive breast cancer is used as an AI steroid structure (92). Letrozole (Femera 2.5 mg/30 tablets) and Anastrozole (Arimidex 1 mg/28 tablets) are nonsteroidal AIs. They are triazoles that reversibly bind to the aromatase enzyme by competing with androgens by binding sites (92).

AIs have been used as letrozole and anastrozole severe pain related to endometriosis (93, 94). However, the hypoestrogenic environment is formed by GnRH analogs and AI drugs that cause symptoms of menopause (hot flashes, vaginal dryness, arthralgia, etc.) and bone loss (osteopenia, osteoporosis, and fracture) (95). Also, AIs can lead to cardiovascular toxicity, lipid profile changes, fatigue, forgetfulness, and sleep disorders (96). The drug prescription is 1 mg once a day in anastrozole or 2.5 mg orally once daily in letrozole (97). These drugs are recommended only in menopausal women but in combination with other anti-ovulation medicines in pre-menopausal patients. AIs induce gonadotropin release with negative feed-back and can occur functional cysts by stimulating follicular development. Studies showed that more functional cysts were observed in 24.3% of women who used 2 mg/day of letrozole alone for two months compared to the triptorelin group (82). Another study conducted premenopausal stage IV endometriosis patients showed that letrozole 2.5 mg/day and desogestrel 75 µg/day used for six months, functional ovarian cysts with a greater diameter of 5.0 ± 1.3 cm were presented in all patients. More than one ovarian cyst developed in 66.7% of patients (98). In these patients, bilateral oophorectomy or ovarian suppression with GnRH analogs may be necessary, especially malignant tumors (99). In premenopausal patients, analog treatment of GnRH or supplementary COCs is recommended to suppress

follicular development. 5 mg oral norethindrone acetate (NETA) per day is another alternative for these patients (100).

A systemic review (82) examining AIs indicated that letrozole protocols 2.5mg/day were proposed (6 months in 8 studies, 2 months in 1 study, 12 months in 1 study) or 5mg/day for 3 months or 0.25 mg/day orally + 2g vaginally were used (82). In addition, Anastrozole used 1 mg/day for 3 or 6 months (82). Patients with osteopenia were not enrolled in these studies. Although all patients used calcium and vitamin D therapy, bone mineral density (BMD) decreased significantly after treatment (82). In particular, in patients who were administered GnRH in addition to AIs, a greater reduction in BMD was observed. Besides, NETA or COCs adding therapy to diminish BMD was not observed (82). Therefore, the use of NETA or COCs may be recommended as additional first-line therapy to reduce adverse effects of AIs (formation of functional cysts, symptoms of menopause, decreased BMD) (82).

Besides, the use of AIs vaginally as effective as the lower dose and associated with fewer side effects (82). Especially in patients with rectovaginal endometriosis, the benefits provided by the local effect are significant. Studies had shown that when 10 rectovaginal endometriosis premenopausal women used 0.25 mg vaginal anastrozole (with calcium and vitamin D) for 6 months, patients with chronic pelvic pain and dyspareunia were stable. Still, dysmenorrhea was significantly reduced, and plasma gonadotropin and estradiol were fixed, and osteopenia was not occurred (101). Another study showed that using a vaginal ring containing AIs may be another alternative treatment method (82).

The effectiveness of AIs was first reported to reduce pain symptoms due to severe endometriosis a patient undergoing hysterectomy and bilateral salpingo-oophorectomy (102). In some cases, it has been reported that AIs are effective postmenopausal relapses and safe

for postmenopausal breast cancer development (103). In a systematic review of premenopausal patients, the combined use of progestin, COCs, or GnRH analogs with AIs reduced the size and pain scores of the lesions (104). A randomized controlled study concluded that using GnRH analogs significantly reduced pain, especially when compared to GnRH analog alone (104). In this study, it was observed that the recurrence time of symptoms was longer in patients receiving combination therapy, and similar results were found between the groups in terms of quality of life and changes in BMD (104). However, in another non-randomized study, the combination of letrozole and NETA administration in patients with rectovaginal endometriosis and pain was more effective than NETA alone in reducing pain and deep dyspareunia. Still, combined treatment was associated with an adverse effect and a higher cost (105). When letrozole and NETA or combinations of letrozole and triptorelin to each other, a similar decrease was observed in both combinations (106). It showed a greater reduction in endometriotic nodules in the group receiving letrozole and triptorelin. However, treatment-related adverse reactions such as arthralgia, loss of libido, heat flushes, and depression increase (106). Also, there was a statistically significant decrease in BMD observed in the triptorelin group (106).

In conclusion, it has been reported that AIs reduce estrogen production in all tissues and may be more effective than drugs that inhibit estrogen production only from the ovary. It can be a good alternative treatment option, especially for patients who do not benefit sufficiently from progestin, GnRH analogs, and COCs. However, AIs are still in its infancy, and its use is limited (82). To reduce the side effects of AIs, it is recommended to be combined with NETA or COCs during AI usage (82). However, the most appropriate add-back treatment (including calcium and vitamin D) has not been clearly defined when using AIs. It should not be

forgotten that the use of AIs in combination with NETA treatment has more side effects, even if it is more effective in reducing pain and decreasing the volume of endometrioma than using only NETA (82). Letrozole 2.5mg / day + NETA 2.5mg / day is the most studied and effective use for six months (82). To overcome this uncertainty, the treatment can be shaped according to aromatase enzyme presence in the specimen in patients undergoing surgery. Also, AIs may be a good option in patients with peripheral estrogen production, such as obese and postmenopausal women. However, before these drugs using the patient should be informed, there is no indication for endometriosis disease in the drug package insert of AIs. In the future, the benefit of patients from AIs may rise that define the most appropriate dose, appropriate add-back treatment, new ways of using, and the duration of treatment.

5.2.Danazol

Danazol, a 17 alpha-ethinyltestosterone derivative, inhibits the growth of endometriotic systems with effects such as removal of gonadotropin secretion, inhibition of ovarian estrogen production and steroidogenesis, and an increase in free testosterone levels (107). Besides its androgenic effect, danazol has also been shown to induce cytotoxicity of apoptosis and affect the expression of proteins that regulate apoptosis in leukemia cells, leading to apoptosis induction in chronic lymphocytic leukemia (108). Danazol is a synthetic steroid metabolized in the liver and reaches maximum plasma concentration within 2-8 hours of oral administration of a 400 mg tablet(109). Danazol was used to treat endometriosis and other gynecological diseases such as myoma uteri, fibrocystic breast disease, and menorrhagia and has shown more efficacy for this treatment than other medical treatments such as progestogens, NSAIDs, and oral contraceptives (109). Nowadays, it is used in various hematological diseases such as persistent/chronic immune thrombocytopenia (ITP),

amegakaryocytic thrombocytic purpura, paroxysmal nocturnal hemoglobinuria, myelofibrosis, and hereditary angioedema that do not respond to corticosteroids or other treatments. Danazol is commenced 50, 100, and 200 mg oral tablets and 100 or 200 mg twice daily for mild endometriosis and 400 mg twice daily tablets for moderate to severe endometriosis. Side effects may be observed at doses above 200 mg per day for a long time (109). Treatment is usually administered orally at divided doses ranging from 400 to 800 mg daily for six months (109). A systematic review of five studies involving women with histopathologically confirmed endometriosis, six months of danazol therapy was considered more effective than placebo at pain relief associated with endometriosis (110). Furthermore, in Cochrane, only GnRH analogs, levonorgestrel intrauterine secretory system (LNG-IUS and danazol treatment were considered effective in treating endometriosis and pain (111). In this review comparing the analogs of GnRH and danazol, no differences were observed between the GnRH analogs in the reduction of dysmenorrhea (RR 0.98, 95% CI 0.92-1.04). Still, when all pain-related complaints were evaluated, the analogs of GnRH were higher than danazol (RR 1.10, 95% CI 1.01 to 1.21) (111). Farquhar et al. found that danazol treatment (including its use in addition to surgery) was effective in alleviating endometriosis pain compared to placebo (mean difference (MD) -3.4, 95% CI -4.8 to -1.8). However, they indicated that there had been an improvement in laparoscopic scores, while women taking danazol were more likely to have side effects (11). In another study, improvement in pain scores proved effective enough to continue for six months after cessation of the treatment (112). An improvement in the symptoms with vaginal danazol has been reported in a systematic review, especially in women with rectovaginal endometriosis (113).

Although Danazol effectively treats pain associated with endometriosis, it is not widely used due to its androgenic side effects. Side effects such as acne, muscle cramps, edema, weight gain (5% of body weight), abnormal vaginal bleeding in the form of spotting, hirsutism, and voice thickening have been reported (110). Furthermore, several studies have highlighted the concern about increased ovarian neoplasia in endometriosis patients treated with danazol (114, 115). The reason for this is reiterated, given several reports of cancer-related mutations (CAMs) in the disease, that the use of danazol may create a "negative selection" in favor of CAM-bearing endometriotic cells and thus increase ovarian neoplasms (115). To reduce these side effects, methods such as vaginal danazol or an intrauterine device containing danazol may limit systemic androgen effects and reduce pain scores, but further research is needed (113, 116). Moreover, caution should be exercised when using danazol with other drugs that cause hepatotoxicity, especially in the geriatric and diabetic populations, as it may cause liver damage and rhabdomyolysis with statin-derived drugs used in hyperlipidemia (109).

In conclusion, GnRH analog or COCs therapy seems beneficial in addition to AIs treatment of endometriosis in premenopausal patients. It has been reported that AIs treatment is merely sufficient in controlling pain and recurrence in postmenopausal patients. On the other hand, Danazol has historically been utilized in treating endometriosis, but it has been used in hematological diseases more recently. Although Danazol treatments are helpful in some specific cases, common usage of Danazol is limited due to its substantial side effects.

6. New Medical Treatment Options in Endometriosis

There are different degrees of success rates for medical treatments used to treat endometriosis. A variety of side effects may occur with the long-term use of existing treatments. Besides, there are relapses after discontinuation of treatments. Therefore, the

search for more reliable and effective new treatments with fewer side effect profiles continues. These include anti-angiogenesis treatments, statins, TNF-alpha blockers, PPAR-γ inhibitors, and various treatments such as pentoxyphiline. (50)

6.1. Anti-Angiogenesis Factors

Angiogenesis plays an important role in the formation of endometriotic lesions. In literature, angiogenic factors are secreted from endometriotic lesions, such as vascular endothelial growth factor (VEGF), and peritoneal fluid is also rich in angiogenic factors. Theoretically, preventing the formation of new blood vessels could stop the growth of new lesions, and old lesions could regress. With this idea, various studies are being carried out to understand the role of anti–angiogenic factors in endometriosis treatment. (117) TNP-470 (analog of fumagillin), Endostatin (a proteolytic fragment of collagen which has endogenous anti-angiogenic activity), Anginex (a synthetic peptide stopping the growth of blood vessels and induction of apoptosis), and an anti-VEGF agent such as Avastin antibody is successful in reducing the size of lesions in animal models. However, data on human studies are limited. It has been shown that Dopamine receptor 2 agonists Cabergoline and Quinagolide reduce angiogenesis by dephosphorylation of VEGF2.

In the mouse model, treatment with an ergot-derived dopamine agonist (Cabergoline) and a non-ergot dopamine agonist (Quinagolide) effectively inhibited angiogenesis and reducing the size of endometriotic lesions. (118) In the study by Gomez et al., 9 women with hyperprolactinemia associated with endometriosis were examined. (119) These women first underwent a surgical procedure in which half of the endometriotic lesions were excised, and the other half marked.

Kinagolid was given for 18-20 weeks, and then a second laparoscopy was performed. A significant reduction in the lesion size and the ratio of VEGF / VEGF2 levels of proangiogenic cytokine and plasminogen activator inhibitor (PAI-1) has been noted.

6.2.Statins

Statins typically used in hypercholesterolemia treatment are a group of drugs that lower cholesterol levels by blocking the enzyme that converts 3-hydroxy-3 methylglutaryl - coenzyme A, a precursor for cholesterol, to be alone. It is thought that they can be used in endometriosis due to their anti-inflammatory, antiangiogenic and antioxidant effects. Atorvastatin, simvastatin, mevastatin, and lovastatin have been tested in in vitro tissue cultures and animal models of endometriosis. (120) Sharma et al. reported increased inhibition of inflammatory and angiogenic genes (COX-2, VEGF, RAGE, and en-RAGE) in endometriotic cells treated with atorvastatin. They also reported that the expression of anti-inflammatory genes (PPAR-γ and LXRa and IGFBP-1) increased. (121) In another study, simvastatin has been shown to cause a dose-dependent decrease in matrix metalloproteinase-3 (MMP-3) and reduce the number and size of endometriotic lesions in a mouse model. (122)

It is thought that statins can be used in the treatment of endometriosis due to their anti-inflammatory, antiangiogenic and antioxidant affects.

6.3. TNF Alpha Blockers

TNF alpha, a proinflammatory cytokine, was found to be increased in peritoneal fluid in women with endometriosis, directly related to the disease stage. Agents targeting TNF alpha have been used successfully to treat inflammatory conditions such as rheumatoid arthritis and

Crohn's disease. Infliximab, a monoclonal antibody against TNF alpha, and etanercept, a fusion protein capable of neutralizing TNF alpha, are being actively studied in endometriosis treatment. In animal models, treatment with these agents has been shown to reduce the size and number of endometriotic implants, reducing inflammatory cytokine levels. (123) However, there is little evidence for the effectiveness of these agents in humans. More studies are needed to fully understand the scope of these agents in the treatment of endometriosis.

6.4.Peroxisome Proliferator-Activated Receptor Gamma Ligands (PPAR-γ)

PPARs are ligand-activated nuclear receptors that play an important role in inflammation, lipid, and glucose metabolism. PPAR-ligands have anti-inflammatory properties and decrease estrogen biosynthesis by inhibiting the aromatase enzyme activity. In experimental models, they have been shown to inhibit cell proliferation, increase apoptosis, and inhibit the growth of endometriotic lesions by affecting the angiogenic factor VEGF. (124) Rosiglitazone and pioglitazone reduce the volume, weight, and size of endometriotic lesions in animal models. Although human studies continue, there are concerns about the cardiovascular side effects of derosiglitazone.

6.5.Pentoksifilin

Another agent that has been recently studied in the treatment of endometriosis is pentoxifylline. Pentoxifylline, currently used in caludicasio intermittent treatment, improves the vascular structure in stenotic arteries by inhibiting the phosphodiesterase enzyme activity. It also suppresses the release of inflammatory mediators by blocking TNF alpha. It is effective in improving fertility and reducing the size of lesions in endometriosis mouse models. (125) Human studies are limited, showing no significant improvement in pelvic pain or clinical pregnancy rates in women treated with pentoxifylline, based on a meta-analysis.

(126) Current evidence does not support the routine use of pentoxifylline in endometriosis-related pain or infertility, and further research is needed. In conclusion, various therapies are thought to be used to treat endometriosis, such as anti-angiogenesis treatments, statins, TNF-alpha blockers, PPAR-inhibitors, and pentoxifylline. Although successful data have been obtained from the ongoing trials, more reliable studies are needed for these agents to be used in daily practice.

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