WWW.IJRPR.COM

International Journal of Research Publication and Reviews

Journal homepage: www.ijrpr.com ISSN 2582-7421

A Review on Advances in Hormonal Therapy for Endometriosis

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ABSTRACT:

Endometriotic lesions have been linked to hormonal abnormalities, including progesterone resistance and the upregulation of estrogen production and metabolism. Increased proliferation, inflammation, pain, and infertility are the outcomes of this hormonal imbalance. Hormonal abnormalities are the focus of treatment. The new hormonal medications and therapy strategies for endometriosis are growing. Hormonal Substances Hormonal medications that operate on the estrogen receptors and reduce both local and systemic estrogen production (GnRH agonists, GnRH antagonists, aromatase inhibitors) or action (selective estrogen receptor modulators).

Background: *Over the past ten years, there has been a significant shift in the field of hormone therapy for endometriosis. Novel selective progesterone receptor modulators, oral GnRH antagonists, and medications that target inflammatory pathways and estrogen production are promising alternatives with improved safety profiles and greater treatment flexibility.*

Method: *Additional papers were discovered by manually examining the reference lists of significant research and relevant reviews. Publications that improved our understanding of therapeutic mechanisms included clinical trials, observational studies, systematic reviews, meta-analyses, and significant preclinical research. We took into consideration studies that evaluated hormonal treatments for lesion activity, overall disease burden, or symptom management.*

Conclusion: *The advancement of artificial intelligence and its advanced data processing capabilities provide a great opportunity to revolutionize endometriosis diagnosis and treatment.*

Keywords: Endometriosis, estrogen, GnRH agonist, GnRH antagonist, Aromatase inhibitor, proliferation, inflammation, selective estrogen receptor modulator, lesion activity.

1. INTRODUCTION:

About 10% of women who are of reproductive age suffer with endometriosis, a persistent illness with no recognized cause. Infertility and persistent pelvic pain are the primary signs of endometriosis. One-third of women who endure infertility and up to 40% of infertile women endometriosis during a laparoscopy for persistent pelvic pain . Chronic pelvic pain has a significant negative social and economic impact due to its impairment and suffering (1). Endometriosis develops through a variety of processes, such as cell growth and differentiation, apoptosis, migration, adhesion, invasion, inflammation, and neuroangiogenesis . A fundamental factor in this condition is the altered expression of estrogen (ER) and progesterone (PR) receptors in endometriotic tissue. Additionally, significant amounts of sex steroid hormones are produced locally in endometriotic tissue, which further impacts themechanism of endometriosis progression. Consequently, the most commonly used treatments for endometriosis focus on targeting ER or PR. The effect of endometriosis is very chronic and it affects various aspects of a patient's life, including work, social interactions, relationships, emotional well-being, and sexuality, ultimately leading to a reduction in quality of life. Furthermore, it significantly influences women's mental health, as many experience high levels of depression, anxiety, and alexithymia; thus, there's a pressing need for new treatment approaches (2). Transvaginal ultrasonography is considered the best technique for diagnosing deep endometriosis and ovarian endometriomas. When gynecologists are not experienced in ultrasonographic diagnosis or when ultrasound results are unclear, magnetic resonance imaging (MRI) may come in handy. For a definitive diagnosis of endometriosis, surgery followed by a histological examination remains the gold standard. While treating endometriosis, there are a few options available, including conservative or more extensive surgery, as well as medical therapies. While surgery can definitely help alleviate pain linked to endometriosis and enhance quality of life and sexual function, it can be quite complex and comes with potential risks, including complications involving the organs, blood vessels, and nerves. For most women dealing with endometriosis, medical therapy is often the first approach taken, focusing on reducing pain symptoms and preventing recurrence of the disease after surgery (3). So, there are quite a few signs that suggest endometriosis is dependent on estrogen. However, it seems that the regulation of endometriotic tissue by estrogen isn't as straightforward as it's for endometriosis (4).

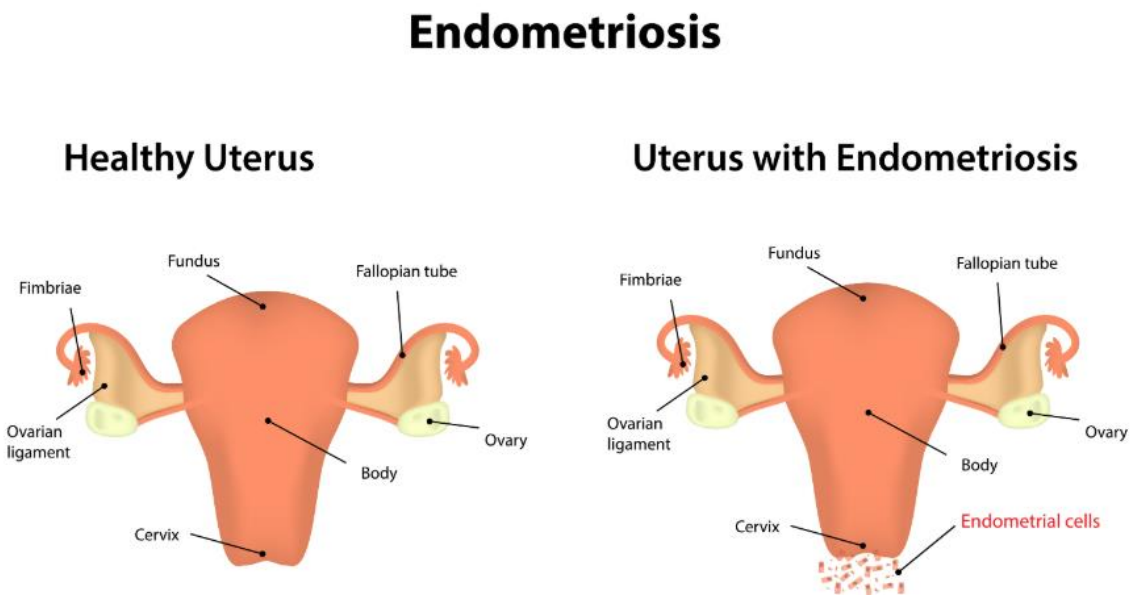

Figure 1: Endometriosis

2. GnRH Analogues

Goserelin, nafarelin, buserelin, and triptorelin have been shown to be effective for managing pain associated with endometriosis . The use of GnRH analogs for pain management has been recognized for two decades as the gold standard; however, it is now classified as a second-line option when first-line treatments are ineffective, poorly tolerated, or contraindicated. Administering GnRHa after surgery may be beneficial in alleviating pain and preventing recurrence of symptoms in patients who have not received complete treatment (5). From a practical perspective, managing patients with endometriosis-related pelvic pain requires multiple rounds of medical therapy. The initial treatment involves the continuous use of combined oral contraceptives (COCs) to induce amenorrhea, in conjunction with nonsteroidal anti-inflammatory drugs. Should there be no noticeable improvement, it would be prudent to consider the use of the levonorgestrel-releasing intrauterine system (LNG-IUS) or gonadotropin-releasing hormone agonists (GnRHas) as a second-line treatment. The LNG-IUS represents a safe and effective long-term therapeutic option for a duration of up to five years (6). The concept of inhibiting endometriosis before commencing ovarian stimulation for IVF has also been applied through the administration of danazol or gestrinone . Nevertheless, no significant difference was observed in pregnancy rates after a pretreatment period of 6–9 months when compared to patients with untreated endometriosis (21% vs. 15%) (7). Therapy using GnRH analogs has certain limitations, such as a significant recurrence rate, with 50% of patients experiencing a relapse of symptoms within six months following the cessation of treatment. Additionally, there are side effects related to the temporary pharmacologic menopause condition induced by this therapy, which include loss of bone density, deterioration of serum lipoprotein cholesterol distribution, hot flashes, genitourinary atrophy, depression, and a reduced libido (8). Currently, the majority of medical therapies for endometriosis function by inhibiting the hypothalamo-pituitary-ovarian axis and are consequently contraceptive, making them unsuitable for women who wish to become pregnant. It has been suggested that undergoing a GnRH-a treatment for a duration of 3 to 6 months could result in a subsequent increase in fertility following the cessation of the treatment (9).

3. Gonadotropin-releasing hormone agonists

Gonadotropin-releasing hormone agonists (GnRH-a) are likely the most widely utilized treatment medications for endometriosis in the USA and are regarded as the gold standard for medical therapy. Multiple administration routes are available, including intranasal, subcutaneous, and intramuscular methods, with depot intramuscular administration being the preferred choice due to its monthly or trimonthly scheduling (10). GnRH agonists should not be used during pregnancy due to reports of fetal abnormalities and a higher rate of fetal mortality observed in animal studies. While these agonists typically suppress ovulation, effectively preventing pregnancy during treatment, this is not a guaranteed outcome. Therefore, patients are advised to utilize a reliable method of birth control while undergoing treatment (11). There are six distinct GnRH agonists that can be utilized for the medical treatment of endometriosis. Among these, three are decapeptides (nafarelin, goserelin, and triptorelin), while the other three are nonapeptides (buserelin, leuprolide, and histrelin). Each agonist is available through one or more different methods of administration (12). Gonadotropin-releasing hormone agonists (GnRH-a) are synthesized from the natural gonadotropin-releasing hormone (GnRH) through the alteration of one or more amino acids. This modification helps them resist breakdown by endopeptidase, which extends their half-life and leads to a longer duration of receptor occupancy (13). The usual side effects of GnRH-a are tied to the symptoms caused by the significant hypoestrogenemia. These symptoms encompass hot flushes and night sweats, issues with sleep, dryness in the vaginal area, as well as a reduction in bone mineral density (14). Growing evidence suggests that a certain amount of normal ovarian tissue is removed alongside the endometrioma wall during laparoscopic cystectomy for endometriomas, which leads to a reduced ovarian reserve (15). Several clinical trials have compared GnRH-agonists to either no treatment or a placebo. One randomized controlled trial (RCT) found that a 6-month

course of intranasal buserelin (administered at 1,200 µg per day) significantly alleviated pain symptoms when compared to expectant management in infertile patients diagnosed with endometriosis. Additionally, four RCTs examined the effectiveness of LEU and TRP against placebo. In a 1998 double-blind RCT, TRP was administered at 3.75 mg monthly and compared to placebo in a group of 25 women with surgically confirmed endometriosis; it was observed that TRP was more effective than placebo in reducing pain symptoms among 28 participants (16). It was proposed that giving a small dose of sex steroid hormone along with the GnRH agonist could maintain the effectiveness of the treatment while reducing or removing side effects. The anticipated outcome would be better adherence to the medication and continued use throughout the whole prescribed treatment period. This hypothesis has indeed been validated (17). Gonadotropin-releasing hormone agonists are effective in managing symptomatic endometriosis. These medications seem to reduce serum and peritoneal cytokine levels and might promote the return of endometrial markers related to implantation (18).

4. Gonadotropin-releasing hormone antagonist

GnRH stimulates the secretion of both follicle-stimulating hormone (FSH) and luteinizing hormone (LH) from the pituitary gonadotrope cells. GnRH antagonists cause competitive binding to the GnRH receptor, resulting in a quick and reversible decrease in gonadotropin secretion (19). The primary way GnRH antagonists work is through competitive receptor occupancy, leading to the blockage of GnRH receptor dimerization, a necessary biochemical process for activating the receptor. The antagonistic effects of GnRH occur by competing with the body's own GnRH for binding sites in the pituitary (20). GnRH antagonists primarily function by occupying receptors competitively, which prevents the dimerization of GnRH receptors—a crucial biochemical step for receptor activation. The antagonistic action of GnRH arises from its competition with the body's natural GnRH for binding sites in the pituitary (21). Cetrorelix is a GnRH antagonist that comes in the form of a sterile lyophilized powder suitable for subcutaneous injections, which requires reconstitution with sterile water for injection. Following promising outcomes seen in pre-clinical studies, cetrorelix was administered at a dosage of 3 mg subcutaneously each week for two months in a clinical trial involving 15 patients who had been laparoscopically diagnosed with endometriosis (22). There is limited information available regarding the use of GnRH antagonists for treating pain related to endometriosis. Their oral intake among healthy premenopausal women has been demonstrated to promptly reduce LH and FSH levels, which is tied to a dose-dependent decrease in estrogen levels (23). At present, the available formulations of GnRH antagonists necessitate subcutaneous injections at least once a week. Elagolix, which is an orally active, non-peptide GnRH antagonist, has been shown to alleviate pain symptoms related to endometriosis in a randomized, double-blind, placebo-controlled Phase II study (24). Both mifepristone and onapristone, another medication that acts as a progesterone antagonist, have shown encouraging results for endometriosis in rodent studies. Multiple non-randomized small trials have indicated a reduction in pain and a decrease in observable disease during laparoscopy (25). Research conducted in laboratories evaluated how GnRH-antagonists impact endometriosis. The effectiveness of cetorelix in blocking TNF-α-induced cell growth in both endometriotic and endometrial stromal cells was compared to that of buserelin acetate; both therapies reduced the growth of endometrial stromal cells by inhibiting TNF-α. Nevertheless, the size of endometriotic stromal lesions did not diminish following these two treatments (26). GnRH antagonists are recommended as a second or third line of treatment for endometriosis due to their potential side effects, which can include vasomotor symptoms, vaginal dryness, reduced libido, irritability, and a decrease in bone mineral density caused by hypoestrogenism (27).

4.1 Cetrorelix

Cetrorelix is a fundamental peptide GnRH antagonist delivered through subcutaneous injections; it is widely utilized in assisted reproductive technology (ART), although it lacks approval for treating women with endometriosis. An in vitro study examined how cetrorelix compares to a GnRH agonist (buserelin acetate) in inhibiting cell proliferation in both endometriotic and endometrial stromal cells (28).

4.2 Elagolix

Elagolix is a short-acting, nonpeptide GnRH antagonist taken orally, which leads to a dose-dependent reduction in pituitary and ovarian hormones in women. Its oral administration and short half-life of approximately 6 hours facilitate the quick removal of elagolix from the body, a pharmacokinetic feature that could be beneficial if treatment needs to be halted for any reason. At present, phase II studies regarding the use of elagolix in women suffering from endometriosis have been published; a phase III trial is currently enrolling women experiencing moderate to severe pain associated with endometriosis, with an estimated completion date for the study set for November 2016 (29).

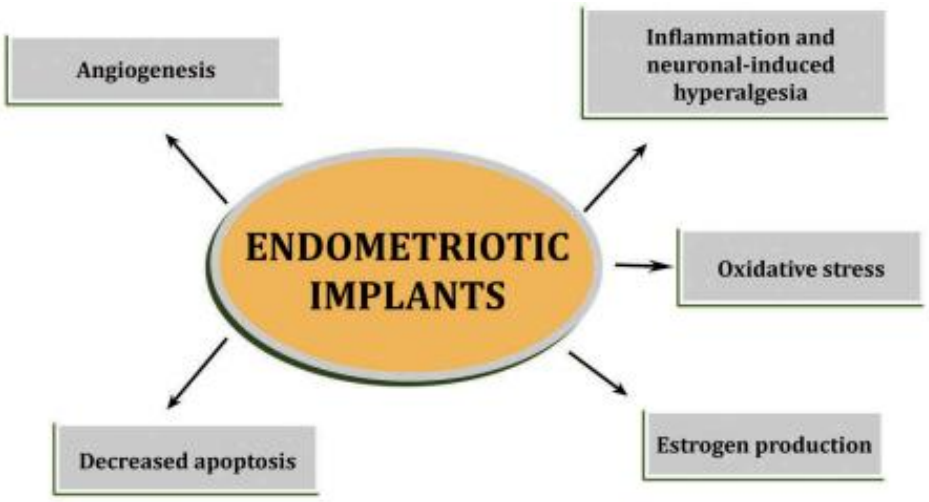

Figure 2: Endometriotic Implants

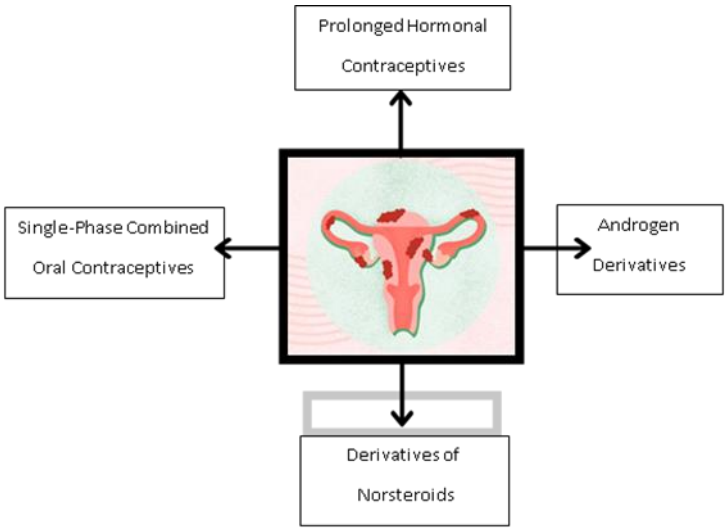

Figure 2: Endometriosis Treatment

5. Aromatase inhibitors

AIs are categorized as type I and type II inhibitors. Both categories of inhibitors vie for attachment to the active site.The enzymatic activity is ultimately halted by an irreversible connection formed between the inhibitor and the enzyme protein.There are numerous powerful and selective third-generation Ais on the market; among them, anastrozole and letrozole stand out with significant benefits over previous agents regarding their effectiveness and tolerability (30). The change of C19 steroids into aromatic compounds is known as aromatization.The synthesis of estrogen involves a crucial step: the creation of estrogens..The P450 aromatase catalyzes this process.

The monooxygenase enzyme complex, found in the endoplasmic reticulum is smooth and serves as a demethylase (31). Aromatization is the conversion of C19 steroids into aromatic molecules.The formation of estrogens is an essential component in the production of estrogen.. This reaction is catalyzed by the enzyme P450 aromatase..The monooxygenase enzyme complex, which is located in the Acting as a demethylase, the endoplasmic reticulum is smooth (32). The most important enzyme for estrogen production is aromatase p-450. since it promotes the conversion of testosterone and androstenedione to estradiol (E2) anestrone.10 Endometriotic lesions and the eutopic are consistently found to express aromatase endometrium from women suffering from endometriosis, as opposed to it being missing from the eutopic endometrium of women who do not have the illness (33). The amount of aromatase is controlled at the levels of protein production, transcriptional expression endometriosis-related expression and enzyme activity.

It participates in a feedback loop that is positive and encourages the way important steroidogenic genes are expressed (34). The majority of therapy-related adverse events are a direct result of estrogen level reduction. By employing negative feedback, AIs cause the release of gonadotropins, which promotes the formation of follicles in the ovaries that have turned into functional cysts due to the lack of ovulation. In fact, it has been suggested that AIs be given for a few days as a replacement for clomiphene citrate in order to recruit follicles (35). Compared to norethisterone acetate by itself, the combination of letrozole and norethisterone acetate was more successful in lowering pain and deep dyspareunia. The use of

AIs appears to lower the likelihood of the pain returning after the surgery (36). Ten clinical investigations on the topic were discovered by our research team during a systematic review of the literature.The treatment of endometriosis with AIs (globally enrolling 183 patients). This is how the administration is handled.The ongoing delivery of LTZ and anastrozole throughout the study period resulted in a reduction in the severity of the review alleviating the pain associated with endometriosis and improving women's quality of life (37). As a result, AIs should be viewed as experimental and should only be taken into account in scientific research settings for individuals who are unresponsive to conventional hormonal therapy. But the treatment of endometriosis may have an intriguing future option in the form of a novel formulation of an AI (anastrozole) and a progestogen (levonorgestrel) delivered in an intravaginal ring, which is now being tested (38). It is interesting that the majority of these aromatase-positive ovarian tumors were of the endometrioid type, even though the significance of aromatase expression (i.e., estrogen production) in epithelial ovarian tumors is currently unclear (39).

5.1 Anastrazole

Anastrozole is a competitive, non-steroidal aromatase inhibitor that competes for binding sites on endogenous aromatase by imitating the typical enzyme substrate. organism. Anastrozol, which is sold under the brand name Arimidex (AstraZeneca), is primarily used to treat metastases in postmenopausal women and breast cancer following surgery. Aromatase has been used to treat endometriosis since it has been suggested that it contributes to the disease's development (40). Amsterdam and colleagues examined fifteen premenopausal patients with proven resistant endometriosis and chronic pelvic pain as part of a wider evaluation of the effects of anastrozole in combination with oral contraceptives. Males were given levonorgestrel (0.1 mg), ethinyl estradiol (20 μg), and anastrozole (1 mg) daily for six months. Every month, pelvic discomfort was evaluated while side effects, blood counts, and bone density were tracked (41).

5.2 Letrozole

Similar to anastrozole, letrozole (marketed under the brand name Femera [Novartis]) is a non-steroidal, competitive aromatase inhibitor that is mostly used to treat breast cancer. Endometriosis has been treated with letrozole either by itself or in conjunction with steroid analogs.. Letrozole treatment for endometriosis patients was initially described in 2004 (42). Ten premenopausal patients with endometriosis were given letrozole (2.5 mg daily) together with progestin and norethindrone acetate (2.5 mg) for six months in that study, which used an open-label, non-randomized design. Prior to and following the start of treatment, pelvic discomfort, endometriosis stage, bone density, serum estrogen, LH, and FSH were assessed. Letrozole administration significantly decreased pelvic discomfort and endometriosis stage, but it had no effect on bone density or blood estrogen levels (43).

6. Selective estrogen receptor modulators

In different tissues, selective estrogen receptor modulators (SERMs) operate as estrogen or anti-estrogen by directly binding to ER-α and/or ER-β in target cells.

One new SERM that effectively prevents osteoporosis and bone loss is bazedoxifene. fractures in postmenopausal women, exhibiting a good endometrial safety profile and neutral effects on the breast (44). SERMs have been suggested as a therapy for endometriosis because of its estrogen-dependent nature. Nevertheless, no SERMs have been shown to be successful in treating endometriosis. SERM is an acronym for a class of medications that affect the estrogen receptor in a certain way (45). New research suggests that endometriosis may be treated with this family of drugs, particularly agonists targeting the b-subunit. Compared to traditional a-SERMs, the b-unit is thought to act on distinct targets, including the endometrium, mammary, and bone (46). Endometriosis-related discomfort is thought to be brought on by a localized inflammatory response that gets worse during the menstrual cycle. Since endometriosis symptoms can be effectively treated with nonsteroidal anti-inflammatory medications,The pathophysiology of pain associated with endometriosis may be significantly influenced by prostaglandins (47). In a number of rat models, SERMs targeting the b-subunit have been shown to have anti-inflammatory effects against several inflammatory-mediated illnesses, including like rheumatoid arthritis and inflammatory intestinal disorders According to one study, 40–75% of mice treated with a SERM targeting the b-subunit had their endometriosis alleviated (48).

7. Selective progesterone receptor modulators

SPRMs are novel ligands for the progesterone receptor that, depending on the target tissue, have agonist or antagonist actions. Through selective inhibition, SPRMs cause amenorrhea. Increased endometrial growth in the absence of the systemic consequences of estrogen deficiency. They also reduce the generation of endometrial prostaglandins, which alleviates discomfort associated with endometriosis. Because SPRMs bind to ER very weakly, they exert an antiproliferative impact (49). SPRMs exhibit strong binding affinity to PR, similar to progestins and progesterone antagonists (antiprogestins). However, in different animal models, the SPRMs have very different effects from either progestins or progesterone antagonists (antiprogestins). The SPRMs function as weak progestins when progesterone is not present (50). Given that both PR-A and PR-B mRNA isoforms are produced from the same PR gene and that the proteins they express have the same ligand and DNA binding characteristics, it is probable that PR A/B homodimers and heterodimers exist. PR-B (116 kDa) is not the same as PR-A (94 kDa) only by a further 165 AA stretch at the protein's N-terminus (51). The first SPRM to move to a clinical stage for the treatment of endometriosis is asoprisnil. Both the menstrual cycle and endometrial development can be suppressed by asoprisnil. There is currently just one published randomized, 130 women with a laparoscopic diagnosis of endometriosis who had moderate to severe pelvic pain at baseline participated in a placebo-controlled study of asoprisnil (5, 10, and 25 mg/day) for 12 weeks (52). When different cell types and growth factor

signaling are involved in tissue-specific interactions, the molecular biology of these diverse impacts becomes clearer. Within Selective steroid receptor modulators (SPRMs) are helpful in gynecology because they attract co-repressors, which in turn prevent some of progesterone's translational effects (53). Both PR isoforms are expressed by the human endometrium at every stage of the menstrual cycle, although the ratio of PRA to PRB and the overall number of receptors vary in response to changes in circulating ovarian steroids, with PRA often outnumbering PRB (54). In certain tissues, especially the endometrium, they may also exhibit mild antiprogestagenic effects when progesterone is present. In contrast to progesterone antagonists, SPRMs very slightly induce labor in mice that are pregnant (55).

8. Immunomodulators

There is growing evidence that the genesis and progression of endometriosis are significantly influenced by altered immunological function. It is now evident that pelvic inflammation. Potential targets for endometriosis treatment and/or prevention include enhanced macrophage activation and extracellular matrix invasion. It is believed that immunomodulators function by reducing the inflammatory reaction to illness (56). Genomic changes may be the secondary cause of the ectopic endometrium's abnormal cellular and molecular activity. Allelic imbalances, loss of heterozygosity, clonal alterations, and aberrant chromosomes were found in the ectopic EC and in cell lines generated from endometriosis. 12–14 Microarray study revealed that the ectopic endometrium had altered cell cycle and metabolic detoxification enzyme gene expression (57). EMS has been linked to an imbalance between T-helper 1 (Th1) and T-helper 2 (Th2), where the pro-inflammatory Th1 profile predominates over the Th2 anti-inflammatory response. One of the major immune system regulators CD4-derived regulatory T cells (Tregs) are involved in EMS activities. The thymus spontaneously produces Tregs, which express the transcription factor Foxp3+ (58). It has been proposed that a lack of cell-mediated immunity allows the implantation of misplaced EC, which causes endometriosis, and hinders the removal of retrograde menstrual waste from the peritoneal environment. On the other hand, endometriosis may be considered an autoimmune illness (59).

9. Side effects

Although they are uncommon, AI side effects can include headaches and diarrhea. AIs can raise the risk of osteoporosis because they reduce estrogen in local tissues. Six months after using an AI, one study observed no improvement in bone density. an oral contraceptive in premenopausal women, while another discovered that after six months of use, AI combined with a GnRH agonist reduced bone density in premenopausal women (60). Gonadotropin releasing hormone agonist (GnRHa) use is known to cause short-term negative effects, which are said to go away three to six months after quitting medication. There have not yet been any stories in the lay media of persistent, irreversible negative effects of treatment conducted a scientific investigation. Our objective was to investigate the possibility of long-term GnRHa side effects in patients treated for endometriosis throughout adolescence with this medicine plus add-back (61). The most popular AI used to induce ovulation is letrozole. For infertility, it is administered cyclically as opposed to continually when used for pain. There is a black box warning about taking letrozole while pregnant, and the FDA has not approved it for this use in female (62). Both premenopausal and postmenopausal women have not had any serious side effects from AI medication. Based on the information at hand, AI administration need to be limited to the few ladies who have significant discomfort in spite of prior hormonal and surgical treatments (63).

10. Future perspective

The paucity of medical therapy options for endometriosis is a difficult element of the condition.Oral contraceptives, progestins,many people may not be a good fit for gonadotropin-releasing hormone (GnRH) agonists because of their negative effects and contraindications (64). A number of novel compounds that operate on various hormonal targets have been developed as a result of advances in our understanding of the hormonal imbalance of endometriosis and its impact on the course of the illness. They include systems that control the hyperestronenic environment and/or the reaction of endometriosis tissue to progesterone (65). Other variables can also affect how people feel about endocrine therapy while dealing with a difficult and long-term chronic condition like endometriosis: Unhappiness with public handling and medical care could cause this survey to be biased since some groups are overrepresented. Furthermore, there are undoubtedly people who struggle to accept their illness and, as a result, typically reject the treatment (66).

11 Conclusion

The pathophysiology of endometriosis and its recurrent and chronic character, which make it difficult to treat and cure, have been extensively studied. The symptoms are effectively managed by current medical treatments. However, after stopping, the symptoms typically return, necessitating further treatments. Promising new treatments need to be carefully assessed for long-term safety, tolerance, and efficacy. Research is currently concentrated on developing novel active hormonal and non-hormonal medications to treat patients with endometriosis.

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