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Updates of Medical Therapy for Endometriosis

Literature Review

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Abstract – Endometriosis is a benign uterine disease characterized by menstrual pain and infertility, which greatly affects women's health. It is a chronic disease that requires long-term care. Hormonal drugs are used for medical treatment and are based on the pathogenetic endocrine component. Estrogen dependence and progesterone resistance are the main causes of ectopic implantation of endometrial cells, reducing apoptosis and increasing oxidative stress, inflammation and neuroangiogenesis. Endometriotic cells express AMH, TGF-related factors (inhibin, activin, follistatin), CRH, and stress-related peptides. Endocrine and inflammatory changes explain infertility, pain, as well as a series of comorbidities that are described in these patients, such as autoimmune (thyroiditis, arthritis, allergies), inflammation (gastrointestinal disease / urinary disease), and mental health. Hormonal treatment of endometriosis aims to prevent menstruation by inhibiting the hypothalamus-pituitary-ovarian axis or by causing pseudodecidualization from amenorrhea, impairing the progress of endometriotic implantation. GnRH agonists and antagonists are effective in endometriosis by affecting the pituitary-ovarian function. Progestins are often used for long-term treatment (dienogest, NETA, MPA) and are used in many areas of practice. Combined oral contraceptives are also used to reduce the symptoms of endometriosis by inhibiting ovarian function. Clinical trials are currently underway for progesterone receptor modulators, selective estrogen receptor modulators and aromatase inhibitors. At this time, all these drugs are considered as the first treatment for women with endometriosis, to improve their symptoms, delay surgery or prevent the recurrence of the disease after surgery. This review aims to provide a comprehensive state of current and future hormonal therapy for endometriosis .

Keywords – AMH , Activin, aromatase inhibitors, CRH, dienogest endometriosis, estrogen , progesterone resistance, GnRH agonist, GnRH antagonist, inflammation , hormones, inhibin, progestin, SERM, SPRM, stress.

I. INTRODUCTION

Endometriosis is a chronic disease characterized by the presence of endometrial tissue outside the uterine cavity, affecting women with pelvic pain and infertility [1]. The prevalence is between 2 and 10% among women of childbearing age, 30 to 50% among women who have not given birth, and 5 to 21% among women with severe pelvic pain [2] . However, true prevalence is uncertain, as estimates vary across population samples and diagnostic methods [3]. The pathophysiology of endometriosis is still an under-researched topic, but the endocrine system and the inflammatory process are well known, recognizing estrogen dependence [4] and progesterone resistance [5]. The main mechanisms involved in the ectopic localization of endometrial cells include retrograde menstrual cycle, vascular and lymphatic circulation, and/or metaplasia/stem cells. The most accepted theory is retrograde menstruation, in which fragments of the endometrium move from the fallopian tubes into the peritoneal cavity, where they implant, spread and invade the pelvic peritoneum. The movement of endometrial cells in the pelvis is physiological, which leads to apoptosis / autophagy and cell proliferation, the elimination process of these cells, while endometriosis patients, hormonal and genetic / epigenetic changes determine of these processes, supports the cell survive , increase in peritoneal invasion. [6]. Increased estrogen receptor activity, estrogen production in endometriosis lesions, and progesterone resistance are determinants of poor apoptosis, reduced immune function, and increased proliferation [7-9]. Therefore, endometriotic cells attach, enter and invade the peritoneum,

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determining the growth of implants and frequent tissue damage and repair [10], neoangiogenesis [11] and neurogenesis [12]]. Fibroblast-myofibroblast transdifferentiation contributes to the production of collagen and fibrogenesis [13], and the insertion of muscle fibers which, combined with chronic inflammation, explains the painful symptoms. Depending on the location of the lesion, three phenotypes of endometriosis are recognized: ovarian endometriomas (AOM) (common, chocolate cysts), superficial peritoneal endometriosis (SUP) and deep infiltrating endometriosis (DIE) (the most severe form develops in depth more than 5 mm below the peritoneal surface and enters the muscularis propria of the bladder or intestine) [1]. In addition, the extraperitoneal area is described, namely the pleura, diaphragm or umbilicus [14], and 30% of endometriosis cases are associated with adenomyosis (inclusion of endometrial stroma and glands in the myometrium) [15, 16].

The main symptom of endometriosis is menstrual pain, namely dysmenorrhea, dyspareunia, dysuria and dyschezia, and non-cyclical pelvic pain can also occur in these patients. Since these symptoms are not specific to endometriosis and can be signs of other gynecological or non-gynecological diseases, diagnostic errors or significant delays in the identification of endometriosis are often reported [17] .Pain and infertility symptoms are associated with psychological stress, low self-esteem and depression, harming physical, mental and social health [18] and reducing quality of life (QoL) [19]. Therefore, these patients, other than changes in the hypothalamus-pituitary-ovarian (HPO), also have changes in the hypothalamic-pituitary-adrenal (HPA) axis and thyroid function, with a connection to inflammation and immune dysfunction.

In the last two decades, there has been an increase in the diagnosis/incidence of endometriosis and its chronic and progressive nature determines the important impact on the quality of life in these patients. . In the past, surgery was considered the definitive treatment, but recent evidence has shown that it does not resolve the pathogenetic process in patients who require long-term care. The goal of treatment is to control pain and increase fertility by increasing the use of medical treatment, and preventing symptoms and the recurrence of lesions, to avoid repeated surgeries [20, 21]. In fact, surgery in women with endometriosis is associated with the risk of urological, intestinal, vascular and neurological problems and pain may recur or persist if there is insufficient removal of the endometriosis lesion [22, 23]. Currently, medical treatment is considered the first treatment for many women with endometriosis, to improve their symptoms, but also to schedule the best time for surgery or treatment with assisted reproductive treatment (ART), or to prevent the recurrence of post-surgery disease. [1, 24, 25]. The choice of the best treatment depends on the severity of the pain, age, desire to conceive, but also on the impact of the disease on the individual's quality of life [26].Currently, hormonal therapy is the most effective drug to treat endometriosis and is based on the pathogenetic process involved in the disease. The goal is to stop cyclical menstruation: by preventing the ovarian secretion of estrogen or by causing the condition of pseudo-pregnancy [21]. Endocrine status supports current and future hormone therapy to treat women with endometriosis.

Endocrine changes in endometriosis

HPO axis hormone

FSH and LH

There was no significant difference in blood levels of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) between women with endometriosis and control women. However, some FSHR and LHR single nucleotide polymorphisms (SNPs) have been identified in patients with endometriosis (27). The FSHR 680Ser-Ser/GG genotype and the “GG/307Ala680Ser” haplotype are common in fertile women with endometriosis, while the presence of the “GA/307Ala680Asn” haplotype reduces the risk of pregnancy and disease progression [28,29]. In addition, the SS (680 Ser/Ser) or AA (307 Ala/Ala) genotype was associated with a reduced risk of developing stage 3 to 4 endometriosis compared to stage 1 to 2 endometriosis [30]. FSHR 680Asn/Asn induces aromatase activity leading to high estrogen levels and proliferation of endometriotic lesions [31]. Among the LHR SNPs, a polymorphic insertion in exon 1 of the LH receptor gene (insLQ) is common in women with endometriosis and infertility, and is thought to stimulate the activity of the LHR, reducing induction effective up to half maximum concentration and increasing cell surface area expression[32].

Estrogen and ER

Although serum estrogen levels in patients with endometriosis do not differ from those of healthy women, it is clear that changes in estrogen play a role in the etiology of endometriosis: estrogen signals are caused by local estrogen accumulation and increased ER. activity in endometriotic cells . Estrogen is an important biological factor that causes chronic inflammation, promoting the survival of endometriotic cells and the development of lesions. Clear data show that endometriotic tissue expresses all steroid genes, including

aromatase, allowing the production of estradiol (E2) locally de novo. [33]. Local E2 levels are increased in endometriosis due to mutations in the aromatase gene CYP19A1 [34] and decreased 17-hydroxysteroid dehydrogenase type 2 (17HSD2), which normally (caused by P4) converts E2 to estrone and -less strong [35, 36]. Endometriotic stromal cells are epigenetically dysregulated and express proteinogenic steroids and enzymes such as steroidogenic acute regulatory protein (STAR) and convert cholesterol precursor molecules to E2. A key event in E2 binding is the recruitment of steroid factor receptor (SF-1) to steroid gene promoters. This is the main event in the synthesis of E2 [37]. A feedback loop links hyperestrogen stimulation to inflammation. : overexpression of cyclooxygenase 2 (COX2) and CYP19A1 increases the local production of prostaglandins and estrogens, causing serious disturbances [38]. The production of estradiol in endometriosis activates ERβ signaling in favor of survival and inflammation of endometriotic tissue.

In terms of changes in ER activity, an excess of ERβ and a disruption of ERα [39 , 40] have been observed in endometriosis. Changes in promoter methylation may be the cause of increased ERβ/ERα in endometriotic cells, since the ERα promoter region is hypermethylated, leading to reduced expression, while CpG islands in the ERβ promoter become hypomethylated, resulting in increased expression [41,42]. Compared to controls, ERα levels are higher in the eutopic endometrium of women with endometriosis, leading to increased estrogen activity and proliferation, which affects endometrial function. ERβ expression was unchanged in the eutopic endometrium of women with endometriosis, although the ERβ/ERα ratio was increased (43). An important role is played by steroid receptors (SRCs) [44], and defining SRC expression in endometriotic lesions has identified SRC-1 as the predominant SRC [45]. Despite the overall reduction of SRC-1, the level of the mutant is increased in animal and human models. This novel SRC-1 isoform in vitro reduces tumor necrosis factor alpha (TNFa)-mediated apoptosis in endometriotic cells, thereby promoting cell survival and invasion and demonstrating disease pathophysiology in vivo (45). In addition, SRC-1 isoform and ERβ may play a synergistic role in promoting cell survival in endometriosis (46). Estrogens play a major role in the implantation of endometriotic tissue in the peritoneum, lesion survival, production of inflammatory factors (metalloproteinase, cytokines or prostaglandins and growth factors) and angiogenesis. ERβ induces proinflammatory pathways, alters the pelvic peritoneal tissue, and produces inflammatory stimuli that stimulate nociceptors in the pelvic tissue, leading to pain [47]. Pathological levels of local estradiol biosynthesis also appear to result in reduced apoptosis of endometriotic stromal and epithelial cells compared to eutopic endometrial tissue (48-50). Estrogens are also involved in the dysregulation of the immune system in endometriotic lesions. Macrophages in peritoneal fluid from women with endometriosis upregulate ERβ expression and, in a mouse model of E2 endometriosis treatment, increase existing lesion macrophages and macrophage emigration factor expression (51, 52).

Progesterone and PR

Circulating progesterone (P4) levels are similar to those found in healthy women. In endometriosis, dysregulation of progesterone symptoms and the inability of the endometrial tissue to respond properly to progesterone exposure are often found in the condition of progesterone resistance. It manifests in endometriosis by failure to activate PR or transcription of P4 target cells in the presence of bioavailable P4 (53). Progesterone resistance has been well established in endometriosis lesions and in the eutopic endometrium of women with endometriosis (54). Since P4 signaling is required to inhibit the proliferation of E2 and promote termination (55), suppression of the P4 response leads to both increased endometriotic lesions and nonresponsive endometrium (33, 56). Changes in the expression of PR nuclear isoforms PR-A and PR-B, steroid receptor coactivators, and multiple downstream effectors in endometriotic lesions and eutopic endometrium of women with endometriosis represent the molecular cause of progesterone resistance. The concept of progesterone resistance was suggested by the finding that in endometriotic lesions PR-B could not be detected and that PR-A was slightly lower than in normal endometrium (57). Promoter hypermethylation and microRNA silencing are potential mechanisms responsible for PR-B loss in endometriosis. Indeed, aberrations in the genetic and epigenetic processes of PR and their targets have been demonstrated (27). Polymorphism of the progesterone (PR) gene may also promote fatigue in endometriosis (58).

Among the polymorphisms identified in the PR gene of endometriosis patients, the PROGINS polymorphism affects ligand binding and the downstream and cellular conditions of endometriosis and contributes to progesterone resistance (59, 60).Furthermore, in endometriotic tissue, P4 does not induce the epithelial expression of 17β-HSD-2 [35], an enzyme that in normal endometrium produces the expression of the enzyme 17β-hydroxysteroid dehydrogenase type 2 (17β-HSD-2), which metabolizes estrogen E2 into estrone. This other deficiency, combined with excessive estradiol production due to poor aromatase activity, contributes to high estradiol activity in endometriosis. P4 also affects the inflammatory pathway, inhibiting the signaling

of members of the kappa light chain enhancer of the B family (NF-κB) protein in endometrial cells. This signaling network has been implicated in endometriosis as a factor leading to the induction and maintenance of endometriosis (61).

Inhibin, activin and follistatin

Inhibins and activins belong to the transforming growth factor (TGF)-ß superfamily and are involved in the regulation of cell proliferation, differentiation, and apoptosis of endometrial cells. Inhibin A, inhibin B, and activin A are detected in the peritoneal fluid of women with pelvic endometriosis, and endometriosis cells express mRNA for inhibin, βA subunits, ßB and activin receptor types II and IIB [62] . α and β A components are expressed in AOM glands and stroma, and inhibin A and activin A dimers are more concentrated in cyst fluid than in peritoneal fluid (63), suggesting that they may be involved in both immersion defects in eutopic endometrium and the development of ectopic sites of endometriosis [64]. Indeed, in human endometrial stromal cells from women with endometriosis, activin A increases the secretion of IL-6 and IL-8 (65, 66). Changes in AOM and endometrial cripto (activin receptor antagonist) and follistatin (activin-binding protein) indicate an altered activin pathway in endometriosis (67). Also, nodal, a growth factor that is well expressed in the tissue that turns and acts through the SMAD protein, showed only mild changes in endometriosis, distinguishing high endometriosis cells from malignant disease (68). Serum activin A and follistatin do not correlate well with SUP or DIE phenotypes and have high diagnostic sensitivity in diagnosing AOM (69).

Anti-Mullerian Antibody (AMH)

AMH is a dimeric glycoprotein from the transforming growth factor-β superfamily and, in addition to its function in the ovary, it expresses the number of preantral follicles that make up the oocyte pool, so AMH levels act as a marker of ovarian reserve (70). A significant decrease in serum AMH levels has been reported in women with AOM compared with age-matched fertile controls (71). On the other hand, the adverse effects of surgical removal of AOM on ovarian reserve, including AMH levels, are well understood (72-74). Therefore, the effect of endometriosis and AOM per se on ovarian reserve is still controversial [72]. In addition, infertile patients with endometriosis have lower AMH levels than women with a primary diagnosis of male infertility [75]. This conclusion is supported by recent data [76] showing that AMH levels in infertile patients with AOM are lower than controls and patients with AMH have both AMH levels is lower in those with AOM. In addition, patients with previous cystectomy had significantly lower AMH levels than patients with AOM who had not undergone surgery. These results suggest that AOM per se is associated with reduced ovarian reserve and that laparoscopic cystectomy may also significantly impair ovarian reserve. However, AOM patients experience a progressive increase in serum AMH levels, which is faster than that of healthy women [77]. Differential monitoring of AMH levels does not decrease in women with endometriosis, including those with AOM one or two, unless they have previously undergone surgery for AOM, based on data from women undergoing surgery and -no information about infertility, thus distorting the results. [72].

The mechanism by which AOM causes damage to the ovarian cavity remains unclear. The inflammatory response to endometriosis [78] can cause microscopic changes in follicular and vascular patterns. In addition, compression of the ovarian cortex surrounded by the cyst can prevent proliferation and lead to follicular loss [79]. However, more studies are needed to elucidate the mechanisms of AOM-induced damage to ovarian reserve. There are few data on the effect of SUP or DIE, without AOM, on ovarian reserve [80], indicating that the effect of extraovarian endometriosis on ovarian reserve is less pronounced than that of AOM.AMH is also produced by eutopic and ectopic endometriotic cells and secreted into the peritoneal fluid (81). AMH treatment in vitro decreases proliferative activity and increases intracellular signaling for apoptosis, suggesting a role for AMH in disease pathogenesis (82-84).

Other endocrine systems

HPA axis and stress hormones

The pain associated with endometriosis and infertility causes a stress reaction: on the one hand, infertility causes family problems and the fear of disappointing social expectations [85, 86], on the other hand, suffering pelvic pain causes cessation of sexual activity and inactivity [87]. , all of which increase anxiety and chronic stress. Since endometriosis also worries about disease progression, long-term health risks and the prospect of having children can be a source of stress [87-89]. In addition, women with endometriosis experience a delay of 4-7 years between the first manifestation of symptoms and diagnosis [90, 91], which can increase the level of stress experienced by the patient. Women with endometriosis and severe endometriosis-related pain (dysmenorrhea, pelvic pain, dyspareunia) generally have a higher prevalence [92]. However, if one part of the surgical treatment

of women's symptoms reduces the perceived stress, women who undergo multiple surgical procedures report that the high level of stress impairs the quality of life [93]. In fact, endometriosis has a negative impact on health-related quality of life and related factors are often associated with painful symptoms [94]. A recent study by Marki et al. reported that physical pain symptoms and emotional regulation difficulties, the latter triggered by psychological stress, reduce health-related quality of life in women with endometriosis (95). In addition, other aspects, such as self-confidence, self-esteem and emotional well-being, which play a role in mental health and anxiety, change in women with endometriosis [96] . Disruption of the HPA axis is found in patients with endometriosis [97] and is associated with a reduced cortisol response, a condition known as hot flashes. Paradoxical hypocortisolism such as adrenal fatigue [98] can worsen painful symptoms by reducing endogenous analgesia associated with stress (stress-induced analgesia) [99] [100]. In support of this hypothesis, the early morning cortisol response to the CRH assay was related with menstrual and nonmenstrual pain in endometriosis (101). Low levels of salivary cortisol are associated with high levels of perceived negative life stress in patients with endometriosis and chronic pelvic pain [102], as well as salivary hypocortisolism, which associated with infertility and dyspareunia but not dysmenorrhea [103]. . On the other hand, higher hair cortisol levels are found in patients with endometriosis compared to healthy women of the same age, parity, education level and BMI [104]. Additionally, elevated cortisol levels have been found in infertile women with endometriosis, particularly those with advanced disease (105). Interestingly, physical and psychological support increases salivary cortisol levels in women with chronic endometriosis pain (106). CRH and urocortin (Ucn) are produced by the endometrium and act locally by changing tissue differentiation (decidualization of endometrial stroma, embryo implantation and monitoring of pregnancy) and inflammation [107] .

Eutopic endometrium overexpresses CRH, CRHR types 1 and 2, as well as urocortin mRNA and protein (108), thus suggesting that the impaired expression of CRH mRNA and 'Ucn associated with altered CRH-R1 activity may affect destructive process and contribute to infertility in these patients. In fact, cultured endometrial cells from endometriosis patients have reduced reproductive capacity, decreasing the secretion of prolactin, CRH and Ucn [108]. The strongest immunostaining for CRH and Ucn was observed in DIE lesions, with increased expression of CRH-R1 and R2 and the inflammatory enzymes PLA2G2A and COX2 (109). Whereas CRH and Ucn significantly increase COX2 expression (CRH-R2 antagonist astressin effect) and endometriotic tissue expresses both Ucn 2 and Ucn 3 (which regulates the secretion of TNF-α and IL-4), the involvement of this stress pathway in inflammation is suggested (110).Higher levels of CRH binding protein were found in the peritoneal fluid of women with endometriosis than in controls, suggesting possible changes in circulating levels (62). Plasma urocortin levels were twice as high in women with AOM, and levels were significantly higher in AOM cyst fluid than in peritoneal fluid and plasma (111). Furthermore, pre-operative Ucn blood tests in symptomatic women undergoing surgery for suspected endometriosis showed that recovered cases had higher Ucn levels than patients without lesions and higher Ucn levels of Ucn1 between endometriosis phenotypes. However, there is no threshold that can distinguish between endometriosis from other disease conditions, so it is not useful (112).

Thyroid hormones

Autoimmune thyroid disease is often seen in patients with endometriosis, suggesting a pathological link between these two conditions (113-115). A relationship between endometriosis and the presence of thyroid autoantibodies is seen, leading to either hypothyroidism or hyperthyroidism. The risk of endometriosis is significantly increased in women who test positive for antibodies against thyroperoxidase (TPO) [114], with a high number of TSHR antibodies, pathognomonic for Graves' disease. , observed in patients with endometriosis [115]. It is not clear whether these antibodies or thyroid hormones play a role in the pathogenesis of endometriosis. Microarray analysis of mild or severe endometriosis confirmed the involvement of thyroid hormone homeostasis and metabolism in the pathophysiology of endometriosis (116). A new ex vivo study [117] on thyroid transcripts in patients with endometriosis described an overestimation of TSHR and a decrease in T3 biosynthesis and accumulation of T4 in ectopic endometrium. It is suggested that direct stimulation of estrogen receptors in endometrial cells by thyroid hormones causes cell proliferation. In fact, in vitro studies have shown that TSH causes the proliferation of endometriotic cells in all controls, and T4 has a direct proliferative effect on ectopic epithelial and stromal endometrial cells, while T3 only occurs on epithelial cells. In addition, thyroid hormones cause ectopic endometrial cells to produce ROS, which can promote, in turn, the proliferation of endometriotic cells (118). Thyroid hormones can also contribute to the pathogenesis of endometriosis by modulating the immune response, because they can activate neutrophils and macrophages to stimulate a proinflammatory environment (119). Therefore, an increase in serum TSH or T4 can be considered as a factor that plays a role in the development

and progression of endometriosis. Chronic pelvic pain and symptoms in endometriosis patients with thyroid disorders support that endometriosis should be carefully considered in patients with comorbid thyroid disease [117].

Clinical results: pain, infertility and systemic effects in endometriosis

Endometriosis is a heterogeneous disease that also appears in clinical presentations. Common symptoms include dysmenorrhea and non-menstrual pelvic pain, which may progress to chronic pelvic pain [17]. have important effects on daily life [120]. Other symptoms associated with endometriosis include dyspareunia, dyschezia, and dysuria, and are associated with DIE lesions (121, 122). Depending on the involvement of the intestines, patients can change between constipation and diarrhea, dyschezia or the presence of blood in stools (especially perimenstrual) [122, 123] or, in the case of urine, dysuria is frequently observed. cyclical macrohematuria or interstitial cystitis [124]. Chest and shoulder pain should be considered when diaphragmatic endometriosis is suspected [125], while endometriosis in the ileocecal or peri-appendicular region has been well associated with abdominal pain, nausea, vomiting and diarrhea [126, 127].

Regarding the pathophysiology of pain associated with endometriosis, nociceptive (including inflammation), neuropathic and the combination of these processes [128], under the influence of hormonal aberrations, anxiety, inflammation and the relationship between peripheral and central nervous system. 129-131]. Neurogenic factors, such as brain-derived neurotrophic factor (BDNF) and growth factor (NGF), are reported to be overexpressed in peritoneal fluid and endometriotic lesions. of women affected [132]. Neurotrophic factors also respond to estrogens, prostaglandins and cytokines and stimulate the growth and development of brain nerve endings [133, 134], especially in DIE, characterized by large nerve fibers [135]. The development of a vicious circle characterized by nociceptor sensitization and local neo-neurogenesis, which is caused by inflammation and immune mediators, is seen in endometriosis [136]. Endometriotic diseases themselves send negative signals to spinal nerves and activate spinal microglia to maintain painful stimulation, leading to central nervous system dysfunction (137). In fact, many central changes are observed: changes in behavior and central response to negative stimuli, changes in brain function, changes in the HPA and autonomic nervous system, and psychological distress [131]. involved in pain modulation and regulation of endocrine function (137-139). In fact, chronic pain and stress in patients with endometriosis can cause many psychological disorders and somatoform disorders are common [140]. Attitudes of anxiety and depression, as well as a high desire for pain relief are common in patients with endometriosis and may enhance pain perception (141, 142). Another common, but often overlooked, symptom in women with endometriosis is chronic fatigue, although the exact mechanism is still not understood [143].

Women suffering from endometriosis have a high rate of progression of the menstrual cycle, although it is not known whether the endocrine system, rare diseases, and inflammatory factors cause the development of these conditions or not. -have a higher effect (144, 145). Increased risk of inflammatory bowel disease (Chron's disease, ulcerative colitis) [146], allergies (allergic sinus rhinitis and food allergies) [147], autoimmune diseases (systemic lupus erythematosus, rheumatoid arthritis) , Sjögren syndrome, multiple sclerosis, fibromyalgia). Women are more likely to be diagnosed with endometriosis, which also causes neuroendocrine-immune disorders [148-153].

Infertility is another major symptom of endometriosis, although the diagnosis of endometriosis does not always indicate infertility. Endometriosis is diagnosed in approximately 30% of women living in an infertile couple [154]. This disease affects fertility through various processes in the pelvic cavity, ovary and uterus [155]. The pelvic cavity is a dangerous place because the chronic heat changes in the peritoneal fluid and the complexity of the common fallopian tube prevent the tubo-ovarian contact and affect the sperm-oocyte interaction; The ovary produces abnormal oocytes, abnormal folliculogenesis and luteal function, and a reduced ovarian reserve from AOM and/or surgery. Also, in endometriosis, the uterus itself exhibits poor endometrial tolerance, mainly due to changes in local growth factors (integrin, LIF, activin, CRH), hormonal disorders (ER and PR) [9] and dysperistalsis of the myometrium, due to the connection with adenomyosis [156, 157]. However, the evidence supporting abnormal endometrial receptivity in endometriosis remains controversial. Chronic endometrial disease, associated with progesterone resistance, estrogen administration, abnormal cell signaling pathways, and decreased key homeostatic protein expression in women with endometriosis, disrupts the receptivity of the endometrium (158). On the contrary, in vitro fertilization (IVF) and egg donation data, other than basic data on endometrial transcriptome signatures, seem to indicate a genetic signature of early endometrial receptivity. window entry is similar between infertile women with and without endometriosis. , which shows that the quality of embryos and oocytes plays a greater role than the endometrial material itself [159].

Hormonal therapy is often used to treat women with endometriosis. The goal is to prevent menstruation by causing the condition of iatrogenic menopause or pregnancy. Current hormonal medical treatment does not completely cure the disease, but it can control pain symptoms to prevent or postpone surgery and manage the disease in the long term [21, 160]. The first line of hormonal therapy includes progestins, while the second line of therapy is represented by GnRH agonists (GnRH-a) and antagonists. The use of combined oral contraceptives (COCs) is common. New hormonal drugs (aromatase inhibitors, estrogen receptor modulators (SERMs), progesterone receptor modulators (SPRMs)) are being investigated for the treatment of endometriosis .

Gonadotropin releasing hormone agonists (GnRH-a)

GnRH-α (goserelin, leuprolide, nafarelin, buserelin, and triptorelin) is a drug that has been used since the 1990s to treat endometriosis. They bind to GnRH receptors and, during the first ten days of treatment, stimulate the pituitary gland to produce LH and FSH [161]. Finally, prolonged exposure to these agents causes suppression of GnRH receptors, thereby reducing LH and FSH levels and inhibiting ovarian estrogen production (Fig. 4). The cause of hypoestrogenism, which follows the amenorrhoic state, leads to the recurrence of endometriotic lesions [162]. Several trials have shown that GnRH-a increases pain associated with endometriosis [163-166] and a meta-analysis of 41 trials comparing the use of GnRH agonists with different methods, treatment methods and administration methods, reports that GnRH-a is more. effective. as effective as placebo and as effective as other progestins in reducing pain [167]. In particular, the administration of GnRH-α for a period of 3 to 6 months before ART in women with endometriosis can increase the chance of clinical pregnancy by four times (168).

However, GnRH therapy is associated with significant hypoestrogenic effects, including amenorrhea, vasomotor symptoms, sleep problems, urogenital atrophy, and increased bone density. Therefore, GnRH-α should be used with caution in adolescent girls, because these women may not achieve the highest bone density [169]. The addition of additional therapy (low COC, estrogens or progestins only, bisphosphonates, tibolone, or raloxifene) can reduce these negative effects, without reducing the effectiveness of pain relief. In addition to complementary therapy, the administration of GnRH-a, initially limited to 6 months, allowed for a longer period [170]. Some clinical trials and studies have shown that additional treatment with GnRH-α and steroids can be effective for 30 months to 10 years [171, 172]. GnRH antagonists

GnRH antagonists inhibit the production of gonadotropin hormones, competing with endogenous GnRH for its pituitary receptors (Figure 4). Unlike GnRH-a, antagonists do not cause a first flare and result in a faster onset of treatment [21]. They also have the advantage of being administered orally due to their non-peptide structure that avoids intestinal proteolysis. Elagolix, a short-acting GnRH antagonist, has recently been approved in the United States for the treatment of acute and chronic pain associated with endometriosis (21). Compared to conventional GnRHa, elagolix, by blocking the endogenous GnRH signal, causes a dose-related suppression of LH and FSH, as well as a change in estradiol levels. Therefore, it helps to relieve the pain associated with endometriosis and avoids severe hypoestrogenism [21]. The FDA approved elagolix for the treatment of pain associated with endometriosis following the results of a second multicenter, double-blind, randomized 3-minute trial [173] that compared two different doses of elagolix (150 mg once daily or 200 mg twice daily two per day) and a placebo. . In both trials, during 6 months of treatment, elagolix significantly reduced dysmenorrhea and non-menstrual pelvic discomfort. Also in menstruating women, a lower number of menstrual days and moderate or severe dysmenorrhea was observed compared to placebo, indicating a reduction in pain despite going before menstruation [174]. Positive results were found in two 3-part fertility studies [175], which investigated the long-term and safety of elagolix for 12 months, reducing dysmenorrhea, non-menstrual pelvic pain and dyspareunia. In addition, treatment with elagolix improves quality of life [175, 176], reduces the use of analgesics [175] and fatigue [177]. Although it inhibits ovarian function in a dose-dependent manner, elagolix, especially at the highest dose, causes hypoestrogenic effects, as hot flashes, BMD decreases, and high levels. Based on these findings, two ongoing phase III trials are evaluating the safety and efficacy of elagolix alone and elagolix plus E2 and NETA for the treatment and management of acute and chronic pain in children. a premenopausal woman with endometriosis over a 24-month period (NCT03343067). . and NCT03213457). More studies are needed to evaluate the effect of the drug on ovarian function, as many pregnancies are reported during treatment with elagolix; therefore, patients should use non-hormonal contraceptive methods during treatment (178, 179).

Relugolix and linzagolix are two new GnRH antagonists, in advanced stages of clinical development for the management of pain associated with endometriosis (180, 181). A 2nd, multicenter, randomized, double-blind, placebo-controlled trial of oral administration of relugolix for 12 weeks demonstrated its efficacy in reducing endometriosis-related pain in a dose-response manner and some adverse events (burn hot, heavy menstruation). bleeding, and irregular periods and decreased bone mineral

density). However, oral relugolix at a dose of 40 mg was generally well tolerated and showed similar efficacy and safety to leuprorelin [180]. A phase 3 extension trial was conducted to evaluate the long-term efficacy and safety of relugolix 40 mg once daily in combination with low doses of estradiol and norethindrone acetate in endometriosis-related pain. A phase 2b, double-blind, placebo-controlled, dose-finding trial of linzagolix was conducted in women with surgically confirmed endometriosis and severe endometriosis-related pain (181). Doses ≥ 75 mg resulted in a higher number of respondents for general pelvic pain, dysmenorrhea, and non-menstrual pelvic pain after 12 and 24 weeks of treatment. Serum estradiol was suppressed, quality of life improved, and the rate of amenorrhea increased in a dose-dependent manner. Decreased BMD (bone marrow) increased in a dose-dependent manner and was < 1% at week 24 at doses of 50 and 75 mg and up to 2.6% for 200 mg. The most commonly reported adverse effects of trial therapy are hot flashes and headache [181]. Progestins

Progestins are compounds with many actions in RA: Reduction of FSH and LH secretion, anovulation, somewhat hypoestrogenic state and amenorrhea which helps to stop endometriosis and prevent dysmenorrhea. In addition, they have an anti-estrogenic effect that causes pseudodecidualization of the endometrium, inhibits the inflammatory response, induces apoptosis of endometriotic cells, reduces oxidative stress, inhibits angiogenesis and inhibits the expression of matrix metalloproteinases [5,26]. All these processes caused by progestin have a beneficial effect on the progression of endometriosis and associated pain. According to the ESHRE guidelines, progestins are considered as the first choice for the treatment of endometriosis [182], because they are as effective in reducing the number and pain as GnRH agonists, and have a low cost and less bad feelings.

Progestins can be given orally, intramuscularly, subcutaneously or intrauterinely [183]. Progestins commonly used for the treatment of endometriosis pain include dienogest (DNG), norethindrone acetate (NETA), and medroxyprogesterone acetate (MPA) (169, 184). DNG is approved in Europe, Japan, Australia and Singapore, while NETA and MPA are currently approved by the United States Food and Drug Administration (FDA). Other progestin treatment options include gestrinone, desogestrel, danazol, etonogestrel implant, and levonorgestrel intrauterine system (LNG-IUS). Side effects of progestins include frequent uterine bleeding/spotting, weight gain, bone loss (especially for long-term use of depot MPA) , and mood changes (such as depression). Although these side effects are common, they do not usually lead to discontinuation of treatment. In general, progestins are not safe and about two-thirds of patients are satisfied with their use for symptomatic endometriosis (185).

Dienogest

DNG, derived from 19-nortestosterone, is the newest progestin available for endometriosis and, according to some evidence, improves endometriosis pain symptoms during long-term treatment (186). Patients undergoing surgery and diagnosed report similar pain reduction, as women with or without prior treatment [187]. Compared with danazol, MPA, and goserelin, DNG is the most effective method for treating pelvic pain associated with endometriosis (188). Furthermore, no effect on bone mineral density was reported compared to leuprolide treatment, maintaining stable bone turnover [189]. Regarding the effect of DNG according to different endometriosis phenotypes, it causes a significant reduction in the diameter and volume of AOM, while the ovarian reserve seems to be preserved [190]. In women with AOM diagnosed by ultrasound and followed for 12 months, DNG reduced AOM volume by 76% compared to baseline. A decrease of 74.05% was observed for dysmenorrhea, 42.71% for dyspareunia and 48.91% for chronic pelvic pain [191]. In addition, DNG alone has been shown to be superior to COC containing DNG in reducing AOM size [192]. A recent study showed that in women with AOM DNG reduces the size of ovarian cysts, is effective in reducing symptoms related to endometriosis after 6 and 12 months of treatment and successfully (193).

DNG is effective in controlling pain caused by rectovaginal endometriosis [194], urinary bladder endometriosis [195, 196] and DIE [197]. In a prospective study involving 30 women with ultrasound findings of DIE (intestinal and posterior fornix) and DNG for 12 months, it was found that the treatment was effective in controlling the pain symptoms associated with DIE (dysmenorrhea, dyspareunia, dyschezia), so. improving quality of life, even reducing the volume of DIE nodules [198].Patients treated with DNG also showed improvement in sexual function [194] and quality of life [187, 199]. In Asian women, DNG treatment reduced the Endometriosis Health Profile-30 (EHP-30) score in all assessed domains, especially the “pain” domain was improved in 78.4% of patients. Patients were diagnosed with surgery and this was described clinically as pain reduction [200]. In a randomized controlled trial in Chinese women with endometriosis, DNG for 24 weeks resulted in a greater reduction in endometriosis-related pelvic pain than placebo, and maintained or improved its effectiveness after 28 weeks of additional treatment (201).

Long-term treatment (60 months) effectively reduced endometriosis-related pain and prevented the recurrence of pain after surgery without adverse effects [202, 203], especially on bone mineral density (BMD) [189]. Therefore, its use as an initial

treatment for the long-term management of chronic pain associated with endometriosis represents an attractive option. Regarding effectiveness and tolerance, a large study conducted in Korea showed that the satisfaction rate is generally good. The most commonly reported side effects were abnormal uterine bleeding (4.1%), weight gain (2.5%), and headache (1.2%). It was found that the number of patients with healthy bleeding increased as the duration of treatment increased, until amenorrhea [204]. DNG is an effective treatment as well as a post-operative treatment to reduce recurrence, avoid recurrence and control pain symptoms. DNG is effective and efficient as a GnRH agonist in adjunctive therapy using 17b-estradiol and NETA for 6 months for preventing the recurrence of pelvic pain after laparoscopic endometriosis surgery (205). In a study of women who underwent surgery for AOM, receiving medical treatment and DNG for 24 months, there was no case of AOM recurrence [206]. In the case of persistent AOM after surgery, early DNG treatment after recurrence shows that it is possible to reduce the risk of repeated surgery, given that after 24 months of After DNG treatment, size reduction [186] and complete resolution of recurrent AOM. and 57.1% [207].

Norethindrone acetate (NETA)

NETA, another 19-nortestosterone, is effective in reducing pain in women with endometriosis. NETA has a strong progestogenic effect and androgenic activity, which can cause side effects due to residual androgenic activity (weight gain, acne and seborrhea) [208]. Continuous administration of NETA (5 mg/day) for the treatment of endometriosis is approved by the US FDA. Low-dose NETA, 2.5 mg/day orally, is considered an effective, tolerable, and inexpensive first choice for symptomatic rectovaginal endometriosis, reducing VAS scores for dysmenorrhea and dyspareunia (209). A pilot study in women with bowel endometriosis showed that low-dose oral NETA determined a significant improvement in the intensity of chronic pelvic pain, deep dyspareunia, dyschezia and the elimination of cycle symptoms related to the cycle (dysmenorrhea, constipation during the menstrual cycle , diarrhea). during the menstrual cycle and cyclical rectal bleeding) [210]. Recently, a long-term study of 5 years of treatment with NETA (2.5 mg/day to 5 mg/day) was good and well tolerated by women with rectovaginal endometriosis, who had Satisfied or satisfied in 68.8% of cases. Due to its low cost and good pharmacological profile, it may represent a good candidate for the long-term treatment of endometriosis [211]. Low-dose NETA has also been found to have fewer side effects, such as unexpected bleeding, compared to long-term COCs, although it has the same efficacy in pain control (212). A comparison of NETA and DNG as the first drug used in newly diagnosed women with endometriosis showed that 58% of NETA users approved the treatment as compared to 80% of DNG users (208). . However, in a population of symptomatic women with "NETA" resistant rectovaginal endometriosis, who have persistent pain, DNG is effective in treating pain and improving quality of life [213]. Medroxyprogesterone acetate (MPA)

MPA is a 17-OH progesterone formulation, such as an oral formulation or a depot formulation, that can be administered intramuscularly and subcutaneously every 3 months. MPA is more effective than placebo [214] and as effective as danazol [215] and GnRH agonists [216, 217] in reducing endometriosis-related pain. depot MPA (dMPA) decreases pain as leuprolide and improves quality of life and productivity. The main concern with the continued use of MPA depot is loss of BMD with increased risk of fracture, due to estrogen deficiency. Therefore, the FDA has recommended that it should be given only if other methods are ineffective or unacceptable, and limit its use to a maximum of 2 years [218]. On the contrary, the American College of Obstetricians and Gynecologists recommends the use of dMPA because the long-term and current evidence shows the recovery of BMD after the discontinuation of dMPA and, given the small increase in complications away, the benefits of using dMPA. pass the risk.

Danazol

Danazol is a derivative of 17α-ethynyltestosterone and has been approved since 1971 by the FDA to treat endometriosis. Its mechanism of action includes inhibition of pituitary secretion of gonadotropins, specific inhibition of ovarian enzymes responsible for estrogen production, modification of immunological activity, inhibition of cell proliferation and inhibition of growth of endometriotic implants (170, 219). Danazol is effective in treating pain associated with endometriosis [220] and its effectiveness seems to be maintained even after treatment is stopped [215]. However, its use is limited by androgenic-like side effects such as seborrhea, hypertrichosis, weight gain, decreased HDL levels, and increased LDL levels [170]. Danazol is given orally (400 to 800 mg/day). Better efficacy and better tolerance have been reported with intrauterine devices loaded with danazol [221] and external restriction control (200 mg/day) [222, 223], especially in women with DIE and rectovaginal endometriosis [224]. A significant reduction of painful symptoms was observed in patients with DIE, with minimal recurrence and reduction of endometriosis lesions [223]. In addition, long-term use of danazol vaginal suppositories has resulted in better control of persistent

pelvic pain associated with pelvic endometriosis without adverse effects (225). Low-dose vaginal danazol (200 mg daily for 6 months) was also effective for the treatment of pain in persistent endometriosis after surgery for severe disease, with a reduction in VAS pain [226]. With the use of low doses and administration methods of the drug, negative effects are often observed and lipid parameters and liver function will not change.

Other progestins

Desogestrel

Desogestrel (DSG) (75 mg/day) is an effective, safe and inexpensive treatment for endometriosis-related pain [227, 228] that has good satisfaction and leads to a better quality of life. GDM treatment of women with symptomatic rectovaginal endometriosis caused a reduction in volume and an increase in bowel symptoms, chronic pelvic pain, and deep dyspareunia. At the 12-month follow-up, the number of satisfied patients was higher among those treated with the desogestrel pill alone than among those taking the estrogen-progestogen combination pill [229]. DSG was also found to be effective in terms of significant improvement in pelvic pain and dysmenorrhea after 6 months of treatment in common endometriosis. Intermenstrual bleeding is the main adverse event reported during GDM treatment [227]. Levonorgestrel intrauterine device (LNG-IUS)

The effect of LNG-IUS on endometriosis has been evaluated in several RCTs. LNG induces endometrial glandular atrophy and decidual stromal changes, decreases endometrial cell proliferation, and increases apoptotic activity. After the first year of use, a 70 to 90% reduction in menstrual blood loss is observed. The LNG-IUS has been shown to be effective in relieving symptoms of pelvic pain caused by rectovaginal and peritoneal endometriosis and reducing the risk of recurrence of dysmenorrhea after reversible surgery [230]. In fact, the use of LNG-IUS after surgery was associated with a lower rate of dysmenorrhea recurrence than remote control [231–233]. Dyspareunia and dysmenorrhea significantly decreased after 12 months of treatment with few adverse effects and low discontinuation rates [234]. A recent study evaluated the effectiveness of LNG-IUS in the treatment of DNG and no treatment after laparoscopic endometriosis surgery. At 6 and 12 months, the number of central pain in the treatment group was lower, and both treatments had a lower recurrence rate than the control group (3.8% and 9.7%, respectively, and 32.5%). In addition, patients with the LNG-IUD had a lower recurrence rate, suggesting that the LNG-IUD is effective in controlling pain and preventing recurrence (235). However, no effect, or a moderate effect, was observed in preventing the recurrence of AOM. In fact, in a randomized clinical trial involving 80 AOM patients undergoing laparoscopic cystectomy followed by six courses of GnRH-a, then assigned or not assigned to LNG-IUD insertion for 30 months, LNG- IUDs can control pain symptoms, too. it is not effective to prevent AOM recurrence [236]. However, a recent meta-analysis of the effectiveness of different hormonal therapies for preventing the recurrence of AOM in women who underwent reversible surgery showed that among the studies, LNG- IUS took first place (237). **Gestrinone**

In a meta-analysis including two small studies, gestrinone treatment was effective in reducing pain (214). the use of gestrinone for endometriosis is restricted due to its side effects. In fact, due to its androgenic, anti-estrogenic and anti-progestin properties, it can cause acne, seborrhea, hirsutism, weight gain, liver failure and osteoporosis [238].

Etonogestrel is released into a subcutaneous implant (ENG implant)

Few data are also available on the use of etonogestrel subcutaneous implant (ENG implant) for the treatment of women with endometriosis, resulting in a positive reduction in dyspareunia, dysmenorrhea and non-menstrual pelvic pain (239, 240). A recent study evaluating the effectiveness of ENG insertion compared to 52 mg LNG-IUS in the management of pelvic pain associated with endometriosis showed that both drugs improved pelvic pain, dysmenorrhea and health-related quality of life in endometriosis [241].

Oral contraceptive compounds (COCs)

COC is currently used for the treatment of endometriosis, but it is often used as an intensive treatment for women with endometriosis, without surgical confirmation of the disease (242). The ESHRE guidelines classify the prescription of COCs to relieve dyspareunia, dysmenorrhea and non-menstrual pain as type B. On the other hand, level C evidence is given to support the use of COCs going n 'front in women with pain related to endometriosis (182). The advantages of using COCs for the treatment of endometriosis include their good tolerance and low cost, but they contain estrogens. COCs reduce menstrual flow, reduce endometriotic adhesions and reduce cell proliferation [243]. Ovarian function is inhibited and the conversion of arachidonic acid into prostaglandins, which reduces pelvic pain and menstrual pain. Although COCs have been widely used in clinical treatment

for decades, given their effectiveness against dysmenorrhea, there is no high level that shows their effectiveness in the treatment of endometriosis. Only two trials [244, 245], both examined in Japan, compared COCs with placebo in women with endometriosis. In these studies, COC treatment was associated with an increase in dysmenorrhea, cyclical abdominal pain, dyspareunia, and dyschezia. However, the composition of COCs used in these studies (ethinyl estradiol 35 mcg + norethisterone 1 mg in cyclic regimen and ethinyl estradiol 20 mcg + drospirenone 3 mg in alternating regimen) may not be readily available in universal and cannot know whether different systems are universal. have different effects. [246].

In a recent systematic review of patient response to medical treatment for endometriosis [247], the number of patients with painful symptoms at the end of treatment was higher with COC, vaginal ring and patch than GnRH-a but it's progestins. Observations that approximately 50% of patients have partial or no improvement in endometriosis symptoms while on COCs [248] and approximately 70% of women have used multiple COCs for pain relief and more than 40% are listed in Between 3 and 10 different COCs. [248, 249] supports the conclusion that this treatment is completely ineffective [250]. Despite the low doses of COCs (20 to 30 μg is about 4 to 6 times the physiological dose of estrogens) and, due to the changes of ER and PR in endometriosis, the administration of COCs can lead to the control of estrogens in face Progesterone resistance [250]. Studies have also shown an increased risk of endometriosis in former COC users (251).Some studies have shown that COCs prevent and reduce the frequency and severity of frequent dysmenorrhea and recurrence of endometriosis after surgery [252-256]. Continuous use of COCs after elective surgery is more beneficial than cyclical use [253, 256, 257]. However, post-surgery COCs have similar [258] or less efficacy in pain relief than GnRH-α [259]. Finally, despite their use as a therapeutic agent, more research is needed to evaluate the role of COC in the treatment of endometriosis-related pain.

1.1. Anti-progesterone theory

In endometriotic lesions, there are no secretory changes during the luteal phase and the different profiles of estrogen receptors (ER) and progesterone receptors (PR) in eutopic and ectopic endometrium indicate that PR, although present, is not work in the sense of leadership. In fact, the concept of progesterone resistance was first proposed in 1997 [260]. Since then, many high-profile papers support this theory .According to Bulun et al. [261,262] and Yilmaz and Bulun [263], the failure of endometriotic stromal cells to produce progesterone-induced paracrine factors may be due to the absence of PR-B. In endometriotic lesions, ERα decreases but ERβ activity increases, leading to a complete loss of PR-B, which cannot induce 17-beta hydroxysteroid dehydrogenase 2 (17β-HSD2). Progesterone receptor status predicts response to progestin therapy [264], as also discussed in a review by Reis et al [265].

Don and Dolmans have investigated the onset of progesterone resistance in older women [266], and inflammation and oxidative stress play a central role in both the pathogenesis of endometriosis and progesterone resistance. Erythrocytes, apoptotic endometrial tissue, and cellular debris in the peritoneal cavity can cause oxidative stress, while iron overload, oxidative stress, and inflammation can result from erythrocyte lysis (267, 268, 269). Cellular iron storage in ferritin and macrophages can reduce its toxicity, but continuous iron delivery to macrophages can overwhelm ferritin's ability to store iron, causing oxidative stress (268,269). Inflammatory factors, cytokines, and interleukin 1 beta (IL-1β) can impair PR activity and contribute to the suppression of progesterone, ultimately leading to an increase in nuclear factor kappa B (NFκB) in the development of endometriosis (265, 266, 270).Genetic factors and epigenetic effects [271,272] and new progesterone inhibitors can affect the quality of progesterone, as discussed in several studies [266,266,23,274,275,276]. In fact, progesterone resistance can be due to many factors, including DNA hypermethylation [266].

1.2. Heterogeneity of lesions

In peritoneal lesions, active red lesions are known to be well infiltrated by stroma-resident macrophages [277]. They are resistant to progestin, which eventually leads to a slight contraction, but not atrophy [260,278,279]. Several differences between eutopic and ectopic endometrium have been identified, which can be explained by different steroid receptor mechanisms [260,262,263,264]. Nisolle and Don [266] first reported the variety of lesions and their intervariability during the luteal phase and Redwine [280] reviewed it in 2002. As discussed in recent articles, the characteristics a history of peritoneal epithelial cell lesions is rarely present in the period. These were found in eutopic endometrium [281,282]. This diversity and intervariability, known for more than 25 years now [266,280], may be associated with progesterone deficiency in endometriotic lesions, as recently studied [261,275].

1.3. The important role of inflammatory Molecules

Inflammation is one of the main mechanisms that cause any disease related to invasion and dissemination [267,270], so endometriosis, which causes cellular proliferation and infiltration, is not an exception in this sense. Macrophages play a major role in this process by presenting antigens to T cells and initiating inflammation by releasing cytokines that activate other cells (277). In the context of endometriosis, their role is important in adhesion, proliferation, vascularization, angiogenesis, neuroangiogenesis and nerve damage [270]. Several growth factors, including fibroblast growth factor, macrophage-derived insulin-like growth factor, platelet activating factor, and vascular endothelial growth factor (VEGF), are more abundant at ectopic sites in patients with endometriosis than in those without. healthy [283,284,285]. . Migration inhibitory factor (MIF) and monocyte chemoattractant protein 1 are the two most potent factors that cause endometriosis-related inflammation. They restore macrophages in endometriotic lesions, promoting their growth and proliferation by releasing proinflammatory cytokines and other growth factors (286,287).

2. From pathophysiology to new perspectives

As our understanding of the pathophysiology of endometriosis progresses, so do our expectations for new non-hormonal treatments for the disease, using non-steroidal anti-inflammatory drugs and agents antiangiogenic take those who go forward. However, there is a long way from the first test to the clinical test. According to Vanhie et al. [288], although many agents have been tested in clinical trials, few have reached the level of clinical research due to the use of inappropriate animal models and the lack of proper study design and reporting. about planning.

2.1. The targeting of inflammation

2.1.1. Prostaglandin E2, cyclooxygenase-2 and tumor necrosis factor-α

In a recent report, Yu et al. discuss the role of prostaglandin E2 (PGE2) in the development of endometriosis (289). PGE2 is an eicosanoid produced by cyclooxygenase (COX)-2, and the increase of COX-2 in endometriotic lesions plays a role in disease progression [40]. whereas IL-1β regulates COX-2 expression in endometriosis. COX-2 cells are more sensitive to IL-1β stimulation in ectopic endometriotic stromal cells than in eutopic stromal cells [290] and the COX-2/PGE2 pathway is associated with endometriosis [291]. COX-2 expression is associated with many transcriptional pathways and involvement in various disease processes, including inflammation, cancer, and resistance to many drugs (291, 292). COX2/PGE2 signaling may also be directly involved in the pathogenesis of endometriosis, including the regulation of ectopic implantation and endometrial growth, angiogenesis, and immunosuppression (290, 291). COX-2 expression is rapidly increased in response to various pro-inflammatory signals and plays an important role in the initiation and progression of endometriosis (292). In women with the disease, COX-2 expression is higher in the endometrial glandular epithelium, endometrial stroma, and peritoneal fluid than in women without endometriosis (293). PGE2 is a regulator of the body's immune response and has two opposing effects: inflammatory or anti-inflammatory. In endometriosis, inflammatory mediators (COX-2/PGE2) are the target of non-steroidal anti-inflammatory drugs (NSAIDs) [289]. However, anti-inflammatory drugs inhibit the activity of COX-1 and -2 enzymes, preventing prostaglandin production. COX-2 inhibitors (celecoxib, rofecoxib and valdecoxib) have been found [270,288], and celecoxib reduces the number, volume and vascularity of endometriotic lesions in mice [294]. Unfortunately, as discussed by Kapoor et al. [270], some COX-2 inhibitors (rofecoxib, valdecoxib) will be withdrawn from the market due to adverse effects, including myocardial infarction and stroke.

Tumor necrosis factor alpha (TNF-α) is a pro-inflammatory cytokine that acts in endometriosis by stimulating cell adhesion and ectopic proliferation [292]. The anti-inflammatory effects of blocking TNF-α by monoclonal antibodies (e.g. infliximab) or soluble TNF-α receptors (e.g. etanercept) have been shown in vivo in animal models and in humans.

D'Hooghe et al [295] examined the hypothesis that recombinant human TNFRSF1A (r-hTBP1) could prevent the development of endometriosis lesions in baboons, an established model for the study of endometriosis. In animals with laparoscopically confirmed endometriosis, inhibition of TNF-α and soluble TNF-α p55 receptors resulted in inhibition of growth and development of endometriotic implants (45). The surface area of endometriotic lesions was found to be smaller and the disease less severe in rats treated with r-hTBP1 (295). In rats that received ectopic transplants of endometrial tissue, administration of r-hTBP-1 resulted in impaired development compared to controls (296). However, in a placebo-controlled trial, Koninckx et al. [47] did not show that infliximab, an anti-TNF-α monoclonal antibody, relieved pain. 2.1.2. NFκB targets in cytokines

Natural killer cells are one of the most important components of the immune system. Their reduced activity in endometriotic lesions is due to their reduced efficiency in removing endometriotic cells from the peritoneal cavity of women [267,270]. NFκB is a transcription factor that regulates innate immunity and regulates cytokine production, DNA and cell survival at the cellular level.

In endometriotic cells, NKκB activates signaling through stimuli such as TNF-α and IL-1β (298). The transcriptional activity of many pro-inflammatory cytokines/chemokines, such as IL-1, IL-6, IL-8, TNF-α, RANTES, MIF, and ICAM1, is activated by NFκB signaling, demonstrating the role of the importance of NFκB in the inflammatory response in endometriosis [299,300]. NFκB signaling is associated with the progression of endometriosis through several factors, including estrogen, progesterone, oxidative stress, and non-coding miRNAs (nc miRNAs), and can regulate the cellular characteristics of endometriotic cells and peritoneal macrophages in the environment. endometriosis. Macrophages activated by NFB release pro-inflammatory cytokines and growth factors involved in increasing levels of nitric oxide synthase, COX-2, IL-1, IL-6, IL-8, TNF-α and VEGF, therefore, drug inhibitors targeting NFκB can. represents a possible treatment. Liu et al [298] have investigated the potential of anti-NFκB drugs for the treatment of endometriosis. There is no doubt that patients with endometriosis show a high level of expression and release of pro-inflammatory cytokines and growth factors, including IL-1, IL-6, IL-8, epidermal growth factor and factors in - hepatocyte growth, and them. ectopic and eutopic processes. endometrium and peritoneal fluid [270]. Among the various drugs that counteract the effects of these cytokines, tocilizumab may be effective in reducing the inflammation associated with endometriosis [301]. Kapoor et al [270] recently published research on drug inhibitors targeting inflammatory molecules, making them key players in reducing endometriosis. Resveratrol regulates the in vitro expression of inflammatory markers in eutopic endometrium, but more so in ectopic endometrium (270). Tocilizumab [301], an anti-IL-6 monoclonal antibody, induces inflammatory lesions in rats. Pyrvinium pamoate [302] targets IL-6 and IL-8 and inhibits their mRNA expression in vitro. Nobiletin [303], acting on NFκB, IL-6 and IL-1β, reduces wound size and therefore pain levels by inhibiting cell proliferation, angiogenesis and inflammation in mice. All these drugs are used only in mouse models or with endometrial cell cultures in vitro.

2.1.3. Chronic and epigenetic diseases

There is increasing evidence that epigenetics and especially DNA methylation regulatory processes play a role in the pathophysiology of endometriosis (304). In the presence of chronic inflammation, immune cells can trigger changes in the epigenetic process, leading to hypermethylation. Among the transcription factors for uterine function, HOXA10 is well known to be associated with endometrial receptivity and progesterone receptor expression, and is hypermethylated in patients with endometriosis (305). A recent study demonstrated the effectiveness of 5'-aza-deoxycytidine (AZA), a DNA methylation inhibitor, on HOXA10 methylation levels in vitro. All this provides important proof of concept and is the basis for the development of future therapies (56). Unfortunately, existing DNA methylation inhibitors, recently approved by the FDA for hematological diseases, are not ready for clinical application in patients with endometriosis. In fact, these drugs can be toxic to the hematopoietic system and intestines, so it is prohibited in patients who want to conceive.

2.2. Reactive oxygen species are targeted

The increase in reactive oxygen species (ROS) associated with chronic inflammation in endometriosis is also due to dysregulation of ROS detoxification pathways [267,268,269,270]. Thus, ROS may function as signaling molecules to maintain the proliferative phenotype associated with endometriosis [267]. They actually act as second messengers of cell proliferation by activating growth-related signaling pathways, such as serine/threonine protein kinase/mitogen-activated kinase/extracellular signal-regulated kinase (RAF/MEK/ERK) , which participates in the increase. in response. to high endogenous ROS levels [307,308]. ERK 1 and 2, which are members of the MAPK family, are located in the cytoplasm and translocate to the nucleus while MEK 1 and 2 work to promote the expression of genes for proliferation, survival, differentiation and cell adhesion. Reduction of ERK 1 and 2 activity by first-generation MEK 1 and 2 inhibitors resulted in reduced proliferation of human endometrial cells in vitro and human endometriotic lesions implanted in nude mice (309). Other agents that inhibit the same pathway have been studied in mouse models of endometriosis (265,270).

Leflunomide, which acts as an inhibitor of tyrosine kinase to suppress NFκB, and sorafenib, a multikinase inhibitor targeting serine/threonine RAF kinases (RAF-1 and B- RAF), has been shown to reduce proliferative activity in ectopic endometrial cells [309, 310, 311]. However, the administration of sorafenib showed conflicting results in terms of anti-proliferative and antiangiogenic effects in rat models of endometriosis [312,313], which may be due to the lack of sensitivity of the animal model

itself. them. The conflict with stromal and endometrial cell regulators in endometriotic lesions can also explain this difference, as ectopic stromal cell proliferation appears to be unrelated to ROS-dependent and ROS-dependent activation of ERK 1 and 2, indicating and other mechanisms maintain cells in a hyperproliferative state (314). . One of them is the phosphoinositol 3-kinase/protein kinase B/mammalian target of rapamycin (PI3K/Akt/mTOR) pathway, which regulates many cellular functions such as growth, survival and metabolism, and plays a central role in ovarian and deep nodular. endometriosis. [315].

Cannabinoid agonists that inhibit both the RAF/MEK/ERK and PI3K/Akt/mTOR pathways can also inhibit proliferation in deep nodular endometriosis [316], clearly demonstrating the involvement of multiple pathways in proliferation and growth and development of lesions. According to Cacciottola et al. [267], some of the drugs referred to have anti-proliferative and antiangiogenic properties already used in humans for cancer indications. However, due to the high risk of negative effects on fertility and the possibility of pregnancy, they are considered to be unsuitable for the treatment of endometriosis, especially in young patients. . Various phytochemicals have also been tested [317,318], Kapoor et al [270] recently published a review of drug inhibitors that target inflammatory molecules, making them key players in the reduction of endometriosis. Resveratrol regulates in vitro expression of inflammatory markers in eutopic endometrium, but more so in ectopic endometrium (20). Tocilizumab [51], an anti-IL-6 monoclonal antibody, induces inflammatory lesions in rats. Pyrvinium pamoate [312] targets IL-6 and IL-8 and inhibits their mRNA expression in vitro. Nobiletin [313], acting on NFκB, IL-6 and IL-1β, reduces wound inflammation and therefore pain levels by inhibiting cell proliferation, angiogenesis and inflammation in mice. All of these drugs are used only in mouse models or with endometrial cell cultures in vitro.

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The increase in reactive oxygen species (ROS) associated with chronic inflammation in endometriosis is also due to dysregulation of ROS detoxification pathways (267, 268, 269, 270). Thus, ROS may function as signaling molecules to maintain the proliferative phenotype associated with endometriosis (267). They actually act as second messengers of cell proliferation by activating growth-related signaling pathways, such as serine/threonine protein kinase/mitogen-activated kinase/extracellular signal-regulated kinase (RAF/MEK), which contributing to the increase. in response. to endogenous ROS levels [307,308]. ERK 1 and 2, which are members of the MAPK family, are located in the cytoplasm and move to the nucleus while MEK 1 and 2 work to promote the expression of genes for proliferation, survival, differentiation, and cellular adhesion. Reduction of ERK 1 and 2 activity by first-generation MEK 1 and 2 inhibitors resulted in reduction of human endometrial cells in vitro and human endometriotic lesions implanted in nude mice (309). Other factors that inhibit the same pathway have been studied in mouse models of endometriosis (265,270).

Leflunomide, which acts as a tyrosine kinase inhibitor to inhibit NFκB, and sorafenib, a multikinase inhibitor that targets serine/threonine RAF kinases (RAF-1 and B-RAF), have been shown to reduce proliferative activity in cells ectopic endometrium [309], 310, 311]. However, the administration of sorafenib showed conflicting results in terms of antiproliferative and antiangiogenic effects in rat models of endometriosis [312,313], which may be due to the insensitivity of the animal model itself. them. Differences in stromal and endometrial cell regulators in endometriotic lesions can also explain this difference, as ectopic stromal cell proliferation does not affect ROS and ERK 1 and 2-dependent activation, indicating that other processes keep cells in a hyperproliferative state . state (314). . One of them is the phosphoinositol 3-kinase/protein kinase B/mammalian target of rapamycin (PI3K/Akt/mTOR) pathway, which regulates many cell functions such as growth, survival and metabolism. [315]

Cannabinoid agonists that inhibit both RAF/MEK/ERK and PI3K/Akt/mTOR pathways can also inhibit proliferation in deep nodular endometriosis [316], clearly demonstrating the involvement of multiple pathways in proliferation, growth and the development of ulcers. According to Cacciottola et al. [267], some of the mentioned drugs with antiproliferative and antiangiogenic properties have already been used in humans for cancer indications. However, due to the high risk of adverse effects on fertility and the possibility of pregnancy, they are considered to be unsuitable for the treatment of endometriosis, especially in young people. . Various phytochemicals have also been tested [317,318], including naringenin, an antioxidant with anti-inflammatory properties that promote apoptosis. Wound growth in endometriosis models has been inhibited by modification of this pathway (20,319,320). Other antioxidants can be found in plants. Studies in mice have shown that c7urcumin can reduce the development of endometriotic lesions, but this has not been confirmed by experiments with human endometrial cells [321,322]. N-acetylcysteine (NAC) showed antioxidant and antiproliferative effects in animal models of endometriosis by regulating the activity of ERK kinase 1 and 2 (323, 324). NAC treatment significantly reduced endometriotic cyst size and endometriosis-related pain [325] in women diagnosed with ovarian endometriosis.

2.3. Consider apoptotic and autophagic pathways in tumor-promoting genes/proteins

The uterus has a system designed to eliminate unwanted cells, thus removing its endometrium under the control of estrogen and progesterone. In normal endometrium, apoptotic proteins increase in the luteal phase, but not in patients with endometriosis, so apoptosis is prevented and endometrial cells can survive and be implanted in ectopic sites [270,320]. One aspect that inhibits the expression of apoptotic proteins is the increase of cytoprotective enzymes, which work in the presence of oxidative stress (267, 270, 320). Autophagic proteins are also important for the survival of endometriotic cells and, in particular, for the recurrence of endometriosis. Apoptotic and autophagic pathways could therefore prove to be promising targets for the creation of new therapeutic alternatives to treat endometriosis (270,320,326).

Recent research hints at the possibility of acting against endometriotic cells via autophagy-apoptosis pathways. In fact, Mao et al. suggested that cir-RNA silencing (007299) promotes apoptosis of ectopic endometriosis cellular sites (327). Sapmaz et al [328] showed that some drugs such as metformin, letrozole and atorvastatin caused apoptosis and anti-inflammatory effects in experimental models of ovarian and peritoneal endometriosis. According to Lin et al study [329], increased ERα signaling and reduced PR-B expression synergistically led to a hypoautophagic state in ectopic endometrial stromal cells, which also prevented their apoptosis. This study showed that the apoptotic effect of SCM-198, a pseudoalkaloid and synthetic form of leonurine, in ectopic endometrial stromal cells obtained by changing the ERA/PR ratio, promotes autophagic activity and by promoting apoptosis.

2.4. Targeting regulators of epithelial-mesenchymal transition

Epithelial-mesenchymal transition (EMT) is a process that occurs in cellular remodeling, during which cells change and become harmful, such as chronic inflammation, fibrosis, and cancer progression. EMT is characterized by progressive loss of the epithelial phenotype and progressive gain of the mesenchymal phenotype. In a recent study by Konrad et al [330], several EMT-specific pathways such as Twist, Snail, Slug, Zinc finger E-box-binding homeobox 1/2 (ZEB1/2), E/N-cadherin , keratins and claudins have been described. Several changes in the expression of markers related to EMT in ectopic endometrium were found, especially in the three types of endometriosis identified, namely ovarian, peritoneal and deep infiltrative disease, compared to l eutopic endometrium. According to Konrad et al [330], only part of EMT occurs in endometriosis, but there is no doubt that EMT is involved in the development of endometriosis. Endometrial cells can change their structural and functional state from a polarized epithelial phenotype to a highly mesenchymal phenotype, with E-cadherin and N-cadherin emerging as key players (267). Two main factors are responsible for the EMT process in endometrial cells: hypoxic conditions and estrogen concentration [325,326].

By targeting 76 genes, Suda et al [331] showed different mutational profiles between epithelial and stromal cells combined with ovarian endometrioma and normal endometrium. They suggested, as Noë et al. [332]. EMT is often considered the main process of cell migration and invasion, but collective cell migration (CCM) has also been identified in endometriotic lesions in baboons and is involved in the pathogenesis of deep endometriosis (333 .334). In CCM, cells attach to the extracellular matrix and migrate as aggregate cells rather than individual cells, thus avoiding EMT.Since EMT/CCM is involved in the development of endometriosis, drugs targeting cell migration can be used for endometriosis. A recent review by Liu et al [335] reported that EMT markers are highly expressed in ectopic endometrium and are associated with estrogen. Antibiotics targeting EMT regulators may

be beneficial for patients with endometriosis. These inhibitors include isoliquiritigenin [336], fucoidan [337], melatonin [338], and 3,6-dihydroxyflavone [339], but have only been tested in murine endometrial cell lines. The same goes for drugs targeting CCM, which have been used only in cancer cell lines. Studies have shown that CCM can be inhibited in cancer cells, and ursolic acid inhibits CCM in glioblastoma (340), gold nanorods and near-infrared light inhibit CCM in breast cancer cell lines (341), and SU6656, an inhibitor of Src , prevents invasion. from melanoma cells by inhibiting CCM (342). However, no research has been done so far regarding endometrial cells or endometriosis in this context.

2.5. Targeted for angiogenesis and neuroangiogenesis

The process of creating new blood vessels and ensuring adequate blood supply is called angiogenesis. One of the most important factors that stimulate angiogenesis is VEGF, which causes the migration of young cells, their vascularization and even invasion. As new blood vessels develop, various growth factors and matrix metalloproteinase (MMP) complexes are expressed. VEGF expression is increased in red peritoneal lesions and peritoneal fluid of patients with endometriosis. [279]. There are other factors that are also important for angiogenesis, such as platelet-derived endothelial cells, endoglin, MIF, ILs, and protein tyrosine phosphatase (270). Some drugs, such as sunitinib, SU6668, SU5416, sorafenib, and pazopanib, prevent by blocking the angiogenic pathway to reduce bone lesions [343,344]. Quinagolide has been shown to reduce inflammation, possibly through the regulation of angiogenesis (345). Dopamine and dopamine 2 receptor agonists promote the endocytosis of VEGF receptors and can reduce neoangiogenesis (346,347). Pellicer et al [346] showed that targeting angiogenesis with dopamine (DA) agonists is a promising strategy for patients with endometriosis. DAs (bromocriptine, cabergoline and quinagolide) negatively regulate proangiogenic pathways but positively regulate antiangiogenic pathways, thereby inhibiting cell proliferation in endometriotic lesions.

Several studies in baboons have shown the critical role of cell migration in the invasion process [348] and suggested that the muscle fibers may be involved in the development and invasion process of endometriotic lesions [333,334,349]. Neuroangiogenesis (the formation of nerves and blood vessels) is thought to play a critical role in the formation and growth of endometriosis lesions. Sun et al [350] showed that endometrial stromal cells isolated from the eutopic endometrium of women with endometriosis can secrete exosomes, which play an important role in the development of endometriosis by regulating neuroangiogenesis. According to the research of Saunders and Horne [351], the relationship between the proliferation of new blood vessels and nerve fibers provides a mechanism that can explain not only the relationship between the presence of ectopic tissue and the path of pain, but also going through relationships. between nerves and immune cells and neuroinflammation. This shows that the muscles are involved in the pathogenesis of endometriosis. Finally, according to a recent study Vannuccini et al. [352]. Inhibition of neuroangiogenesis in deep peritoneal and endometriotic lesions can prevent the proliferation of ectopic glands and invasion. However, as Vanhie et al [288] and Kapoor et al [270] point out, there are still challenges in developing new non-steroidal therapies for endometriosis, where non-steroidal produce hormones that have not yet entered the hospital. useful.

2.6. Estrogen targets

The presence of well-balanced estrogen and progesterone helps maintain the physiology and function of the eutopic endometrium during the menstrual cycle. Estrogen controls the proliferation of the endometrium, while progesterone blocks the effects of estrogen and helps trigger the termination process. Any imbalance between progesterone and estrogen leads to uterine and endometrial dysfunction [266,353]. The lack of RA is evident in the endometriotic lesions, leading to the suppression of progesterone and poor progesterone function, clearly affecting the survival and development of the endometriotic tissue [261,262,263,266].Obviously, the best solution would be to reduce the level of estradiol (E2) just enough to reduce amenorrhea and treat the symptoms, while maintaining sufficient care to reduce the vasomotor symptoms of menopause (mainly hot flashes) and loss of bone mineral density (BMD). 266,353]. Barbieri's threshold concept [354] states that a concentration of E2 in the range of 30 to 60 pg/mL can provide the best compromise between efficacy, tolerance and safety [349]. Knowing that estrogens play an important role in the survival and vascularity of endometriotic implants, it would be appropriate to consider reducing their concentration as a treatment method. GnRH antagonists cause competitive inhibition of the GnRH receptor, which in turn inhibits the production of follicle-stimulating hormone (FSH) and luteinizing hormone (LH), and inhibits the secretion of steroid hormones. ovarian without stimulating the stimulatory effect [353,355]. The main advantage of these new drugs is the elimination of estrogen in a dose-dependent manner (from parts with low doses to complete with high doses) and rapid changes.

As recently reviewed [353], three oral GnRH antagonists, elagolix, relugolix, and linzagolix, have recently produced strong data in a rare, controlled trial for the treatment of pain. related to endometriosis and premenopausal symptoms. One of them, elagolix, is FDA approved for the treatment of pain associated with endometriosis [356,357,358].The plasma half-life (t1/2) of elagolix ranges from 2.4 to 6.3 hours [356,357,358], requiring twice-daily dosing. The efficacy of 6 months of treatment with elagolix is evaluated. Two different doses were tested (150 mg once daily and 200 mg twice daily). Administration of elagolix 200 mg twice daily induced a strong E2 reduction and resulted in a significant improvement in dysmenorrhea and non-menstrual pelvic pain, although at the cost of an increase in hot flashes and a significant decrease in BMD. Studies are ongoing to evaluate the effects of adjunctive therapy (ABT) using elagolix. Linzagolix has a half-life of 15 to 18 hours [353, 359, 360]. Three different doses were studied (75 mg, 100 mg and 200 mg once daily for 24 weeks). Being able to achieve complete suppression of serum E2 up to the postmenopausal level, 200 mg of linzagolix per day is effective in the control of endometriosis-related dysmenorrhea and non-menstrual pelvic pain (one effective unit over 100 mg), but also has a significant effect. effects on dyspareunia and some aspects of quality of life. In addition, a high rate of hypoestrogenic symptoms, including BMD loss ≥3% was observed in some patients after 24 weeks. Obviously, this once-daily regimen will require ABT hormone if used for more than 6 months [359].

Medicines in development for endometriosis

Selective Progesterone Receptor Modulators (SPRMs) SPRMs are progesterone receptor ligands that act as progesterone agonist, antagonist, or partial agonist/antagonist in different progesterone target tissues. Although SPRM prevents ovulation, they are not associated with the process of estrogen suppression, because estradiol secretion is not affected and the distribution of estradiol levels remains within the physiological range. In addition, SPRM inhibits endometrial proliferation, prevents endometrial bleeding through direct effects on endometrial blood vessels, and reduces endometrial prostaglandin production in specific tissue types (21). Therefore, the effectiveness of SPRM in endometriosis [360-362] is suggested, but no SPRM is used in the clinic.

Ulipristal acetate (UPA), telapristone acetate, vilaprisan, and tanaproget are SPRMs approved for the treatment of endometriosis (363, 364). SPRM is generally well received. Common side effects include headache, abdominal pain, nausea, dizziness, and heavy bleeding. Mifepristone and asoprisnil are the most studied SPRMs. Recovery of mifepristone-induced endometriotic lesions is variable and seems to depend on the duration of treatment (365, 366). A small, prospective, open-label trial suggested the potential efficacy of mifepristone for endometriosis-related pain (265). Similar results were observed in phase II/III; However, 3.4% of patients reported a significant increase in liver transaminases [367]. In a randomized, placebo-controlled trial, asoprisnil resulted in a significant reduction in dysmenorrhea in women with endometriosis compared to placebo (368). The effect of UPA on endometriosis lesions and symptoms of treated women was evaluated during a 27-month follow-up period before surgery. In 58% of cases, progesterone receptor modulator (PAEC)-related endometrial changes affect both eutopic endometrium and ectopic lesions; cases reported a reduction in pain and amenorrhea [369].]. However, there is not enough data to allow a clear conclusion on their safety and effectiveness [21].

Selective Estrogen Receptor Receptors (SERMs)

SERMs bind to estrogen receptors (ER-α and ER-β) in target cells and act as ER agonists in some tissues and ER antagonists in others. Therefore, they are recommended for the treatment of endometriosis and are being studied. . Raloxifene (RLX), a widely accepted drug for the prevention and treatment of osteoporosis, has estrogenic effects on bone and antiestrogen effects on endometrium and breast tissue (162). Tested in animal studies, RLX causes endometriosis implant regression [370,371]. In a prospective, two-study [372], patients suffering from pelvic pain associated with endometriosis following surgical treatment were not assigned RLX or placebo for 6 months. However, the study was discontinued a short time because women in the RLX experienced a recurrence of pelvic pain before surgery than the placebo group. Bazedoxifene (BZA) is a novel SERM used for the treatment of osteoporosis [162] and antagonizes estrogen-induced stimulation of the uterine endometrium [21]. In a rat model, BZA reduces the size of endometriotic lesions and reduces the expression of proliferative nuclear antigen and estrogen receptors in the endometrium (373).

Tissue-selective estrogen combination (TSEC) with BZA and conjugated estrogens (CE) reduced the size of endometriotic lesions in a mouse model. Addition of estrogen to BZA did not increase endometrial growth or hyperplasia and did not decrease SERM activity (223). Therefore, TSEC is a potential new treatment for endometriosis that can be highly effective without the side effects of current treatments.SR-16234 is another investigational SERM with antagonist activity on ERα and partial agonist activity on ERβ. SR has a regressive effect on the development of murine endometriosis-like lesions, by affecting cell proliferation,

angiogenesis, inflammation and NF-κB phosphorylation. A recent study of this drug in a small group of women with endometriosis and adenomyosis showed that SR-16234 can reduce pelvic pain and dysmenorrhea [274].

Aromatase inhibitors

Aromatase is expressed in endometriosis lesions and in the eutopic endometrium of women with endometriosis, causing the local secretion of estrogens, which promote the growth and invasion of endometriosis lesions and promote the appearance of pain and inflammation of prostaglandins [375].

Aromatase inhibitors (AIs) inhibit estrogen synthesis both in the periphery and in the ovaries [376]. Some clinical studies have shown that third-generation non-steroidal AIs, such as letrozole and anastrozole, reduce the severity of painful symptoms associated with endometriosis; However, their use is limited by many side effects, such as bone and joint pain, muscle aches, and fatigue [377].

The ESHRE guidelines recommend only the use of AIs in combination with COCs or progestins or GnRH-a in patients with pain resistant to drugs and surgery resistant rectovaginal endometriosis [169]. Currently, a multicenter, randomized, double-blind, parallel-group phase IIb trial is evaluating the efficacy and safety of BAY98-7196 (an intravaginal ring of different anastrozole and LNG), compared to placebo and LEU (subcutaneous storage).). treating women with symptomatic endometriosis within 12 weeks (NCT02203331)

II. Conclusion

The cause of endometriosis remains a source of controversy. Any progress in our understanding of the pathophysiology of endometriosis increases our chances of finding a suitable non-hormonal treatment for the disease, with non-steroidal anti-inflammatory and antiangiogenic agents being taken further. However, there is a long way from the first test to the clinical test.

The cause of endometriosis remains a source of controversy. Any progress in our understanding of the pathophysiology of endometriosis increases our chances of finding a suitable non-hormonal treatment for the disease, with non-steroidal anti-inflammatory and antiangiogenic agents being taken further. However, there is a long way from the first test to the clinical test. Evaluating inflammation, NFκB and cytokines, ROS, apoptotic and autophagic pathways, and tumor-promoting genes/proteins should be the focus of future research. Anti-inflammatory drugs inhibit the activity of COX 1 and 2 enzymes, inhibiting the production of prostaglandins. Pharmacological agents that target NFκB may be potential therapeutic agents, and recent studies have focused on the effect of NFκB on macrophages in various mechanisms and effects. they follow the progression of endometriosis through the release of pro-cytokines. Some drugs with anti-proliferative and antiangiogenic properties are already licensed for cancer patients. However, due to the high risk of negative effects on fertility and the possibility of pregnancy, they are not suitable for the treatment of endometriosis, especially in young people.

Autophagic and autophagic pathways may also be valid targets for the development of new therapies to treat endometriosis. EMT is a critical process by which cells undergo complete transformation and become aggressive, as seen in chronic wounds and fibrosis, as well as cancer progression. Antibiotics targeting these EMT agents may be of great benefit to patients with endometriosis. One of the main factors that stimulate angiogenesis is VEGF, so targeting angiogenesis with dopamine agonists may be a promising strategy. However, as this article highlights, the development of non-steroidal treatments for endometriosis is still a challenge, since non-hormonal agents have not been approved in the regular treatment system. . As progesterone resistance may be due to hypermethylation, investigating demethylating agents to treat endometriosis may be a future research strategy .

Decreasing total E2 levels enough to control symptoms, while maintaining adequate monitoring to reduce menopause issues (which are hot flashes) and BMD loss, may be a good solution. An oral GnRH antagonist results in dose-dependent estrogen reduction, allowing modulation of E2 levels and increasing the possibility of individualizing treatment. Endometriosis requires lifelong care. The goal is to increase the use of medical treatment and avoid multiple surgeries. Medical professionals involved in drug research and clinical trials must obtain and be able to provide a comprehensive view of the effects and effects of existing treatments. Finally, any area that requires further research in terms of the efficacy and safety of treatment should be thoroughly studied in populations around the world.

ABBREVIATIONS

AIs	Aromatase inhibitors
AMH	Anti-Müllerian hormone
ART	Assisted reproductive technologies
BDNF	Brain-derived neurotrophic factor
BMD	Bone Mass Density
BZA	Bazedoxifene
CE	Conjugated estrogens
COCs	Combined oral contraceptives
COX2	Cyclooxygenase 2
CRH	Corticotropin-releasing hormone
CRHR	Corticotropin-releasing hormone receptor
DIE	Deep infiltrating endometriosis
DNG	Dienogest
DSG	Desogestrel
E2	Estradiol
ENG-	Implant Etonogestrel-releasing subdermal implant
ESHRE	European Society of Human Reproduction and Embryology
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
Gn-RH	Gonadotropin-releasing hormone
HDL	High-density lipoprotein
HPA	Hypothalamus–pituitary–adrenal axis
HPO	Hypothalamus-pituitary-ovary axis
IL	Interleukin
IVF	*In vitro* fertilization
LDL	Low-density lipoprotein
LH	Luteinizing hormone
LNG	Levonorgestrel

LNG-IUS	Levonorgestrel intrauterine system
MPA	Medroxyprogesterone acetate
NETA	Norethisterone Acetate
NF-kB	Nuclear factor kappa light-chain-enhancer of activated B cells
NGF	Nerve growth factor
OMA	Ovarian endometriomas
P4	Progesterone
PAECs	Progesterone receptor modulator-associated endometrial changes
PR	Progesterone receptor
QoL	Quality of life
RLX	Raloxifene
ROS	Reactive oxygen species
SERMs	Selective estrogen receptor modulators
SF-1	Steroidogenic factor-1
SNPs	Single nucleotide polymorphisms
SPRMs	Selective progesterone receptor modulators
SRCs	Steroid receptor coactivators
STAR	Steroidogenic acute regulatory protein
SUP	Superficial peritoneal endometriosis
TGF	Transforming growth factors
TNFα	Tumor necrosis factor alpha
TPO	Thyroperoxidase
TSEC	Tissue-selective estrogen complex
TSH	Thyroid stimulating hormone
TSHR	Thyroid stimulating hormone receptor
UCN	Urocortin
UPA	Ulipristal acetate
17β-HSD-2	17β-Hydroxysteroid dehydrogenase type 2

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