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Investigational drugs for the treatment of endometriosis, an update on recent developments

Authors:, Fabio Barra ^{1,2}, Carolina Scala ^{1,2}, Valerio Mais ³, Stefano Guerriero ³, Simone Ferrero ^{1,2}

Institutions:

¹ Academic Unit of Obstetrics and Gynecology, Ospedale Policlinico San Martino, Largo R. Benzi 10, 16132 Genoa, Italy

² Department of Neurosciences, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health (DiNOGMI), University of Genoa, Italy

³ Department of Obstetrics and Gynecology, University of Cagliari, Policlinico Universitario Duilio Casula, Monserrato 09042, Cagliari, Italy.

Corresponding Author:

Simone Ferrero MD, PhD; Academic Unit of Obstetrics and Gynecology, IRCCS AOU San Martino – IST, Largo R. Benzi 10, 16132 Genoa, Italy

Telephone 01139 010 511525

Mobile 01139 3477211682

Fax 01139 010511525

E-mail: simone.ferrero@unige.it

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Abstract

Introduction: Endometriosis is a hormone-dependent benign chronic disease that requires a chronic medical therapy. Although currently available drugs are efficacious in treating endometriosis-related pain, some women experience partial or no improvement. Moreover, the recurrence of symptoms is expected after discontinuation of the therapies. Currently, new drugs are under intense clinical investigation for the treatment of endometriosis.

Areas covered: This review aims to offer the reader a complete and updated overview on new investigational drugs and early molecular targets for the treatment of endometriosis. The authors describe the pre-clinical and clinical development of these agents.

Expert opinion: Among the drugs under investigation, late clinical trials on gonadotropin-releasing hormone antagonists (GnRH-ant) showed the most promising results for the treatment of endometriosis. Aromatase inhibitors (AIs) are efficacious in treating endometriosis related pain symptoms but they cause significant adverse effects that limit their long-term use. New targets have been identified to produce drugs for the treatment of endometriosis, but the majority of these new compounds have only been investigated in laboratory studies or early clinical trials. Thus, further clinical research is required in order to elucidate their efficacy and safety in human.

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1.0 Introduction

Endometriosis is a chronic hormonal benign disease with affects 1-5% of women of reproductive age, and it is defined as the presence of endometrial glands and stroma outside the uterus (1-3). Endometriosis includes three clinically distinct forms: peritoneal implants, ovarian endometriomas (OEs) and deep infiltrating endometriosis (DIE). This disease causes pain symptoms (such as dyspareunia, dysmenorrhea, non-menstrual pelvic pain and dyschezia) and infertility in women of reproductive age. As endometriosis is an estrogen-dependent disease, patient's symptoms are influenced by the cyclical fluctuations of ovarian hormones physiologically occurring in fertile women. Pain symptoms usually regress after menopause; however, the disease can be diagnosed in postmenopausal women undergoing surgery (4). Despite extensive research, the understanding of the pathogenesis of endometriosis remains incomplete (2). Transvaginal ultrasonography is the gold standard technique for the diagnosis of deep endometriosis (5) and ovarian endometriomas (6); magnetic resonance imaging (MRI) may be used when the gynecologists have no experience in the ultrasonographic diagnosis of endometriosis or when the findings of ultrasonography are unclear. Surgery and the histological examination are the gold standard for the definitive diagnosis of endometriosis (7).

The treatment of endometriosis involves conservative or radical surgery, or medical therapies. Although surgery improves endometriosis-associated pain, quality of life and sexual function (8), it can be technically demanding and it carries the risks of visceral, vascular and neurological complications. Medical therapy often represents the first-line management for women with endometriosis, aiming to ameliorate pain symptoms and to prevent post-surgical disease recurrence. The choice of the therapy is based on several factors, such as age of the patients, intensity and characteristics of pain, preference of the patients, desire to conceive and presence of comorbidities (such as migraine) (9). The medical management of patients with endometriosis is challenging due to the need of a tolerable chronic regimen, the partial relief of symptoms that often is obtained with current medical therapies and to the fact that pain recurs after the discontinuation of the hormonal

treatment. Traditionally combined oral contraceptives (COCs) have been the first-line treatment for patients with endometriosis, but currently progestins are increasingly and successfully employed as monotherapy, being efficacious and well tolerated for long-period of time (10). These hormonal compounds are efficacious in controlling symptoms in about two-third of women. Second-line therapy is represented by gonadotropin releasing hormone agonists (GnRH-as), which have a less favorable tolerability profile (9). Thus, research is focusing on finding new alternative therapies for the treatment of to this minor percentage of patients resistant to common first-line hormonal treatments. This review aims to offer the reader a complete overview on last drug development and early investigated targets for the treatment of endometriosis.

2.0 Current medical therapy of endometriosis

Nonsteroidal anti-inflammatory drugs (NSAIDs) are largely used for the treatment of endometriosis; however, there is a lack of high-quality evidence supporting their efficacy in managing pain caused by endometriosis. Furthermore, no evidence shows whether any individual NSAID is more effective than another (11). Finally, women taking NSAIDs must be aware that these drugs may cause unintended adverse effect (AEs).

COCs and progestins are first-line therapies and they are often started empirically without a confirmed surgical diagnosis of endometriosis (12, 13). COCs act promoting a supraphysiologic levels of estrogen due to the high estrogenic activity of ethinyl estradiol (EE), thus causing a decrease of estradiol levels. This condition suppresses ovulation, improving symptoms of women affected (2). The continuous use of progestins as monotherapy inhibits ovarian steroidogenesis with subsequent anovulation and decrease of serum levels of endogenous ovarian steroids, causing decidualization of endometriotic implants. Moreover, progestins are able to locally inhibit inflammatory pathways and response, and cause apoptosis of ectopic endometriotic cells (14).

Overall, these two hormonal medical options enable satisfactory long-term pain control in around two-thirds of symptomatic women (2). The imbalance of estrogen receptor and progesterone

receptor subtypes as well as adhesion molecules may contribute to the mechanisms involved in the resistance of this subpopulation refractory to these first-line hormonal therapies. As there are not biomarkers predictive for this resistance, a dynamic monitoring of response to these drugs is thus warranted in order to switch to other medical options or to discuss the most appropriate time for the surgical option (15).

An accurate diagnostic workup is required prior to administering second-line therapies such as GnRH-as (16). These drugs suppress estrogen ovarian production through the down-regulation of gonadotropin-releasing hormone (GnRH) receptors at pituitary level, suppressing the production and release of gonadotropins. The hypoestrogenism and subsequent amenorrhea cause regression of endometriotic implants. GnRH-as, causing the initial stimulation of the hypothalamic-pituitary-gonadal axis, may cause a surge in estrogen levels that is associated with a worsening of symptoms (flare-up effect). Anyway, it does not represent a major issue whether the treatment is started in the mid-luteal phase (17). However, GnRH-as are responsible of several AEs such as alteration of lipid profile, depression, flushes, urogenital atrophy and loss of bone mineral density (BMD). The intensity of these AEs can be decreased by administering “add-back” therapies with progestins, such as norethisterone acetate (NETA). Progestins as “add-back” therapy tend to be preferred to COCs since in these seconds the estrogenic activity of the dose of EE is too high relative to physiologic levels of E₂ (17).

3.0 Investigational treatments for endometriosis

Endometriosis is a multifactor disease in which estrogens and progesterone play a fundamental role. The development and maintenance of endometriosis depend on the alteration of multiple cell mechanisms, such as the proliferation, apoptosis and invasion capacity. The formation of endometriotic lesions involves also the imbalance of tissue-adhesive properties, the activity of

matrix metalloproteinases and the triggering of an angiogenic response. Moreover, the presence of ectopic implants is associated with overproduction of prostaglandins, cytokines and chemokines (2). Understanding the complex mechanisms of this chronic hormonal disease paved the way to the improvement of currently existing treatment options and the investigation of novel targeted drugs (Figure 1). The following paragraphs will describe different classes of new investigational drugs for the treatment of endometriosis that are currently in pre-clinical and late and early clinical studies (Table 1).

4.0 Hormonal therapies

4.1 Gonadotropin releasing hormone antagonist

GnRH is the hypothalamic hormone that induces pituitary secretion of follicle-stimulating hormone (FSH) and luteinizing hormone (LH). Gonadotropin-releasing hormone antagonists (GnRH-ant) act by binding to the same pituitary GnRH receptor, and, they suppress gonadotropin production. The induced hypoestrogenic state inhibits proliferation and invasion of ectopic endometrial cell. However, differently from GnRH-as, GnRH-ant maintain sufficient circulating estradiol (E₂) levels to avoid vasomotor symptoms or loss of BMD. When starting the therapy, there is a further advantage of GnRH-ant over GnRH-as: they have an immediate onset of action and they rapidly reduce sex hormone levels without the initial estrogen surge (18), not causing flare-up effect. Currently, GnRH-ant are available as injectable formulation and increasingly as oral nonpeptide forms (9, 18).

Cetrorelix (CET) is a basic peptide GnRH-ant administered via subcutaneous injections. Taniguchi *et al.* compared the efficacy of CET and buserelin acetate, a GnRH-a, in reducing the proliferation of endometriotic and endometrial stromal cells obtained from OEs. Both treatments decreased cell proliferation by reducing the levels of tumor necrosis factor- α (TNF- α) in endometrial stromal cells, whereas ectopic endometriotic stromal cells did not respond. Moreover, both treatments did not inhibit TNF- α -induced interleukin (IL)-8 production in endometriotic implants (19). Differently, in

another pre-clinical study on rats with peritoneal implants, the administration of CET or leuprolide for 8 weeks showed similar efficacy in causing the regression of implants size of experimental endometriotic lesions, and in reducing their amount of stromal tissue and glandular tissue (20). K pker *et al.* evaluated CET (3 mg, subcutaneous weekly for 8 weeks) in a clinical trial including 15 patients with symptomatic endometriosis. Among them, 10 women (67%) have endometriosis at rAFS stages III (n=4) and IV (n=6). All the women had a complete improvement of pain during treatment. Although they did not experienced AEs related to hypoestrogenism, 3 women (20%) suffered headache only immediately after initial treatment, and 3 women (20%) experienced uterine bleeding. At a second-look laparoscopy, lesions regression was observed in 60% of patients (9/15) and all the endometrial biopsies performed after the end of treatment showed glandular and stromal atrophy. Only 6 patients (40%) still have rAFS stages III (n=1) and IV (n=5)(21).

Elagolix is an oral short-acting nonpeptidic GnRH-ant. It is the most investigated GnRH-ant in women with endometriosis. A controlled, single- and multiple-dose study with sequential dose escalation including 55 healthy premenopausal women was assessed the safety and pharmacokinetics of elagolix. Elagolix was well tolerated and rapidly bioavailable after oral administration; it caused a rapid decline in serum gonadotropins and E₂ concentrations. Daily (50-200 mg) or twice-daily (100 mg) administration for 7 days maintained low E₂ levels (17 ± 3 to 68 ± 46 pg/ml) in most subjects during late follicular phase, which were rapidly reversed after discontinuation (22). Subsequently, a phase II trial by Diamond *et al.* evaluated elagolix (150 or 250 mg once daily for 12 weeks) in comparison to placebo in 155 patients with surgically confirmed endometriosis. Elagolix caused a reduced level of dysmenorrhea and dyspareunia at weeks 8 and 12 compared to placebo, but no significant difference was observed for chronic pelvic pain. Moreover, BMD was minimally but significantly reduced after the hormonal therapy (23). In a randomized double-blind study, with 24-week treatment and 24-week posttreatment period, Carr *et al.* compared the efficacy of elagolix and depot medroxyprogesterone acetate-subcutaneous (DMPA-SC) in 252 women with endometriosis-related pain. Elagolix was found to have minimal

impact on BMD over a 24-week period and showed similar efficacy on pain compared to DMPA-SC (24).

In a recent publication, Taylor *et al.* reported the results of two multicenter double-blind, randomized, placebo-controlled phase 3 trials (Elaris Endometriosis I and II) (25). In both, elagolix (150 mg once daily or 200 mg twice daily) was compared with placebo in 1285 women with surgically diagnosed endometriosis and moderate or severe endometriosis-associated pain. In the first study, the percentage of women who had a clinical response with respect to dysmenorrhea and chronic pelvic pain were 46.4% and 50.4% in the lower-dose elagolix group, 75.8% and 54.5% in the higher-dose elagolix group, 19.6% and 36.5% in the placebo group ($P < 0.001$ for all comparisons). In the second study, the percentage of women who responded to dysmenorrhea and chronic pelvic pain were 43.4% and 49.8% in the lower-dose elagolix group, 72.4% and 57.8% in the higher-dose elagolix group, 22.7% and 36.5% in the placebo group ($P < 0.001$ for all comparisons). Moreover, women receiving elagolix had higher rates of hot flushes (mostly mild or moderate), higher levels of serum lipids, and greater decreases from baseline in BMD than did those receiving placebo.

Currently, two ongoing phase III trials, are evaluating the safety and efficacy of both elagolix alone and elagolix plus E_2 and NETA over 24 months of treatment for the management of moderate to severe pain in premenopausal women with endometriosis (NCT03343067 and NCT03213457).

Other GnRH-ants are currently under investigation. Relugolix (TAK-385) is a new non-peptide, orally selective GnRH-a. After having demonstrated the continuously and reversibly suppression of the hypothalamic-pituitary-gonadal axis (26), it is being tested in clinical trials. A randomized, double-blind, placebo-controlled phase trial III is testing the efficacy and safety of relugolix (40 mg, once-daily) co-administered with either 12 or 24 weeks of low-dose E_2 (1.0 mg) and NETA (0.5 mg), compared with placebo in women with endometriosis associated pain (NCT03204318).

Among other novel drugs, a prospective, dose-finding, randomized, parallel group, double-blind, placebo-controlled phase IIb study is testing the efficacy and safety of OBE2109, another GnRH-

ant, for the treatment of 330 women with moderate-to-severe endometriosis associated pain (NCT02778399); the results are awaited.

4.2 Aromatase inhibitors

The endometriotic tissue expresses all the genes needed to produce estrogens, differently from eutopic endometrium. Aromatase P450 is a critical enzyme responsible of the conversion of androstenedione and testosterone to estrone and E₂ (27). Elevated levels of aromatase mRNA have been demonstrated in ectopic endometriotic implants (28). Based on this background, aromatase inhibitors (AIs) have been investigated for the treatment of women with endometriosis, showing to decrease E₂ level and to reduce endometriotic implants growth and invasion (29).

In a systematic review, Ferrero *et al.* identified ten clinical trials investigating the use of AIs for the treatment of endometriosis (183 women). This review demonstrated that the continuous administration of two AIs, anastrozole and letrozole, was effective in reducing the severity of endometriosis-related pain symptoms and ameliorated women' quality of life (30). However, the use of AIs was limited by the high incidence of AEs. The ESHRE guidelines suggest the therapy with AIs in combination with COCs, progestins or GnRH-as in women with rectovaginal endometriosis, refractory to other medical or surgical treatment (31).

Hefler *et al.* evaluated the administration of anastrozole in a vaginal suppository for the treatment of 10 patients with histologically confirmed rectovaginal endometriosis. After 6 months of treatment, the patients had a significant improvement in dysmenorrhea and quality of life. The volume of the rectovaginal nodules decreased in three patients, remained stable in three and increased in three (32). Currently, a randomized, double-blind, parallel- group, multicenter phase IIb study is assessing the efficacy and safety of BAY98-7196, an intravaginal ring with different dose combinations of anastrozole (300-600-1050 µg/d) and levonorgestrel versus placebo and leuprolide acetate in women with symptomatic endometriosis over a 12-week treatment (NCT02203331). The administration of these hormonal combination by vaginal route may be particularly effective in

women with rectovaginal endometriosis. In fact, a local administration in close proximity to the endometriotic nodules could result in higher concentration of the drug in this localization (33). Another ongoing randomized parallel phase IV trial is evaluating the combination of anastrozole plus leuprolide acetate for the prevention of endometriosis recurrence compared with leuprolide acetate as monotherapy (NCT01769781).

Letrozole is AI most frequently investigated for the treatment of endometriosis. A randomized prospective open-label study including 35 women with rectovaginal endometriosis demonstrated that the intensity of both chronic pelvic pain and deep dyspareunia were significantly lower after 3 and 6 months of therapy when compared with baseline values in patients receiving letrozole in combination with NETA or triptorelin. In addition, more patients treated this double regimen rated their treatment as satisfactory or very satisfactory (64.7%) as compared with patients receiving letrozole and triptorelin (22.2%; $p = 0.028$). Moreover, there was a greater reduction in the volume of endometriotic implants in patients receiving both letrozole and triptorelin than in those receiving letrozole and NETA (34). A prospective, non-randomized clinical trial including eight patients who received a 12-month treatment with letrozole and NETA demonstrated similar results for the reduction of the volume of the rectovaginal nodules infiltrating the rectum. Moreover in this study, there was no increase of more than 5% in the volume of the nodules (35).

The combination of letrozole and NETA has also been tested for the treatment of OEs. In a prospective patient-preference study, the mean percentage reduction in OEs volume was greater in patients receiving the double regimen ($-74.4 \pm 4.2\%$ and $-46.8 \pm 3.8\%$, respectively, $p < 0.001$) than in those receiving only the progestin. However, in both groups, there was not a complete regression of OEs (36). In another small study, five reproductive-age women with recurrent OEs and chronic pelvic pain received a 6-month treatment with letrozole, DSG and EE after a previous failure of surgery and hormonal approaches. During this study, two patients had complete regression of OEs after 3 and 6 months, respectively. Moreover, no recurrences were reported during the follow-up of 2 years (37).

AIs have also been used for preventing the recurrence of endometriosis after surgical treatment, but the results are controversial. Two randomized controlled trials demonstrated that the post-surgical administration of AIs as monotherapy or in combination with GnRH-as decreased more the risk of recurrence of endometriosis when compared with single GnRH-as or danazol (38, 39). However, in another randomized controlled trial, the use of AIs for 2 months after surgery did not succeed in decreasing the risk of disease recurrence in comparison with GnRH-as or placebo (40).

4.3 Selective estrogen receptor modulators

Selective estrogen receptor modulators (SERMs) directly bind to estrogen receptor (ER)- α and/or ER- β in target cells, exerting estrogen- or anti-estrogen-like actions.

Bazedoxifene is a third-generation SERM that is effective in preventing BMD loss and osteoporotic fractures in postmenopausal women, and it does not cause negative effects on breast or endometrium (41). Its activity of antagonizing estrogen stimulation on endometrial cells has led this drug to be investigated for the treatment of endometriosis. In a pre-clinical study on mice, the treatment with bazedoxifene for 8 weeks cause a significant reduction in the size of endometriotic lesions. Moreover, proliferating cell nuclear antigen mRNA and estrogen receptor mRNA expressions were decreased, demonstrating an high inhibition of estrogen-mediated cell proliferation (42). In another pre-clinical study, bazedoxifene in association with conjugated estrogens succeeded in causing regression of endometriotic implants. The authors showed also a reduction in stem cell recruitment to the endometriotic lesions (43). Another group investigated the efficacy of bazedoxifene as monotherapy in comparison with conjugated estrogens on ectopic endometrial implants of mice affected by experimental endometriosis, not founding significant difference in size of lesions between the two groups after the end of the therapy (44).

In a pre-clinical study, the use of raloxifene (10.0 mg/kg), another SERM, in mice with induced-endometriosis, obtaining a significant implant regression (45). Moreover, another randomized, placebo-controlled, single blind trial evaluated its efficacy in comparison with anastrozole,

concluding that both hormonal therapies obtained a similar lesions decrease (46). These promising results led to the investigation of raloxifene in 93 women with endometriosis. A randomized controlled trial, including patients with histologically confirmed endometriosis (ASRM stage I-IV) and chronic pelvic pain, evaluated a 6-month therapy with raloxifene (180 mg, daily) or placebo. This study was interrupted prematurely because patients belonging to the raloxifene group experienced worsening of pain. Moreover, women receiving raloxifene underwent second surgery for endometriosis significantly sooner than those in the placebo group. It has been assumed that raloxifene in human, differently from rodents that have an estrous cycle, may not prevent ovulation. Thus, subsequent ovarian estrogen production may continue and, in some cases, increase in response to the action on receptors of this drug, worsening patients' symptoms (47).

4.4 Selective progesterone receptor modulators

Selective progesterone receptor modulators (SPRMs) bind to the progesterone receptor to block or modify downstream its effects inducing amenorrhea through selective block of endometrial proliferation without the systemic effects of estrogen suppression (48). It is known that SPRMs may induce endometrial changes known as progesterone modulator-associated endometrial changes (PAECs). From available data, these induced endometrial alterations do not seem to be precursors of precancerous lesions, reverting back to normal within 6 months after ending the treatment (49). Mifepristone and other SPRMs antagonize estrogen activities in the endometrium of primates (50-53), induce endometrial atrophy and amenorrhea in ovariectomized, estrogen-substituted monkeys (50, 53-61) and reduce the size of endometriotic implants in primate model (53).

A prospective open-label trial assessed the endocrine and clinical responses to the administration of mifepristone for 3 months for the treatment of 16 women with endometriosis. It caused an improvement of pelvic pain in all patients without significant changes in the extent of implants, assessed by laparoscopy after the end of the treatment (56). Subsequent studies confirmed these

findings demonstrating not only an improvement in endometriosis-related pain symptoms, but also a regression of the lesions (55, 57).

Asoprisnil, another SPRM with a partial agonist/antagonist progestin activity, is under investigation for the treatment of endometriosis. It is known from studies on primates that this drug causes the suppression of endometrial proliferation and promotes amenorrhea by targeting the endometrium (58). In an *in vivo* rat model, asoprisnil did not succeed in reducing of the volume of OEs (60). In a randomized placebo-controlled trial this drug (5, 10, and 25 mg) demonstrated a higher decrease of dysmenorrhea-related to endometriosis in comparison with placebo (61). Anyway, the trials on this drug were stopped for the presence of some cases of endometrial hyperplasia (62). Thus, at the moment very limited evidence is available on the use of asoprisnil for treating endometriosis and better-designed studies are mandatory to investigate its safety and efficacy.

Among the other SPRMs, ulipristal acetate (UPA) has been investigated in this setting, demonstrating to be able to cause the regression and atrophy of endometriotic lesions in rodents (63). Although it is known from clinical trials for treating uterine fibroids that UPA may be responsible of mild to moderate AEs (headache, breast tenderness and hot flushes) (64), recently four cases of serious liver injury (three of which ended in liver transplantation) have been reported. Therefore, in December 2017, the Pharmacovigilance Risk Assessment Committee of the European Medicines Agency (EMA) has started to evaluate whether this drug could be the cause of liver injury. Currently, no clinical data on UPA for the treatment of endometriosis are available.

Tanaproget, another SPRM, succeeded in causing the reduction of endometriotic implants in rodents, but no clinical trials have been never organized in human (65).

5.0 Anti-angiogenic drugs

Angiogenesis is a fundamental mechanism involved in the development and growth of endometriotic implants. Thus, there is a solid rationale to study drugs targeting the angiogenic pathway for the treatment of endometriosis (66).

Vascular endothelial growth factor (VEGF) is the most important molecule involved in angiogenesis (67, 68). Bevacizumab is a recombinant humanized monoclonal antibody that blocks angiogenesis by inhibiting serum VEGF (69). In the murine model, it inhibits the development of endometriotic lesion, decreasing cell proliferation and increasing apoptosis, and reduces vascular density and VEGF levels in peritoneal fluid (70). Another recent pre-clinical study demonstrated that bevacizumab is as effective as GnRH-as in inducing apoptosis of ectopic endometrial cells, and, thus, the regression of lesions (38, 71). It was recently shown that the administration of oral rosuvastatin and intraperitoneal bevacizumab in rats causes a higher regression of implants than oral progesterone compounds (72).

Tyrosine kinase inhibitors (TKIs) inhibit the catalytic activity of tyrosine kinases receptor, such as VEGFRs, platelet-derived growth factor receptors (PDGFRs), and stem cell factor receptor (c-KIT), which are all deeply involved in angiogenesis (73). In a pre-clinical study, sorafenib succeeded in reverting proliferation, migration and neoangiogenesis of ectopic mesenchymal stem cells obtained from ectopic and eutopic endometrial tissue (74). Moreover, it was effective without affecting ovarian reserve in mice with endometriosis (75). A comparative study in the rat model investigated the effects of other TKIs on endometriotic tissue morphology and histological characteristics as well as on ovarian reserve. At the end of the treatment, the endometriosis score was significantly decreased in rat treated with pazopanib versus other investigated drugs and by sunitinib versus sorafenib and normal saline but not by sorafenib. A similar reduction of the VEGF score was achieved using pazopanib, sunitinib, and sorafenib compared to normal saline. Moreover, ovarian follicle number was not significantly affected by any drug evaluated in the study (76). The efficacy of sunitinib on endometriotic lesions compared with no medication or danazol was tested in another

pre-clinical study. Both sunitinib and danazol decreased the volume and the extent of rats' implants, the severity and total score of adhesions due to the disease (77).

Mammalian target of rapamycin (mTOR) is a protein kinase that critically controls cellular growth, proliferation, and survival. Rapamycin, a bacterial macrolide, inhibits this pathway, excreting also anti-angiogenic activity (78). In the animal model, rapamycin decreased the size of the endometriotic implants. Moreover, it inhibited VEGF-induced angiogenesis, as indicated by the suppression of endothelial cell sprouting in vitro and the reduction of microvessel density in implants (79). Temsirolimus and everolimus, two inhibitors of mTOR/AKT pathway, showed to decrease endometriotic cell proliferation both in vitro and in a mouse model (80, 81).

Among other anti-angiogenic compounds, TNP-470, a synthetic analogue of the antibiotic fumagillin, significantly decreased the microvessel density and the number of endometriotic lesions in the chicken chorioallantoic membrane (73). ICON is an immunoconjugate molecule which selectively binds tissue factor, an important modulator of angiogenesis in endometriosis (82). ICON decreased the size of endometriotic implants by exerting vascular disruption without causing apparent toxicity, reducing fertility, or exerting teratogenicity (83).

It has been demonstrated that the important role of dopamine (D) and its receptor 2 in the modulation VEGF-mediated angiogenesis in endometriosis (84-86). For this reason, the administration of D-receptor 2 agonist has been proposed in animal models and women (87-89). Cabergoline and quinagolide, nonergot-derived dopamine agonists, succeeded in decreasing the size of endometriotic lesion of mice, inhibiting angiogenesis (87). Moreover, an experimental study conducted in female nude mice demonstrated that the treatment with cabergoline reduced active endometriotic lesions and cellular proliferation index, decreasing neoangiogenesis. At morphological level, significant changes in gene expression and a lower degree of VEGFR-2 phosphorylation than in controls were demonstrated (88). Currently, an ongoing pilot phase II study is evaluating the efficacy and safety of cabergoline in association with NETA for the treatment of endometriosis-associated pain in women with endometriosis (NCT02542410).

A proof-of-concept study tested the efficacy of quinagolide, administered in a titrated manner (25-75 µg/d) for 18-20 weeks, for decreasing the size of peritoneal lesions in women with endometriosis. This drug induced a decrease of 69.5% in the lesions size. At second-look laparoscopy, the histologic study demonstrated tissue degeneration, with a down-regulation of VEGF/VEGFR2, three proangiogenic cytokines (CCL2, RUNX1, and AGGF1) and plasminogen activator inhibitor-1, a potent inhibitor of fibrinolysis (89).

6.0 Inhibition of inflammation

Cyclooxygenase (COX) is the enzyme responsible of the metabolic conversion of arachidonic acid to PGs. PG-E₂ is a major mediator of inflammation and angiogenesis. The ectopic endometrial tissue is characterized by overproduction of prostaglandins, cytokines and chemokines (2). Non-selective NSAIDs have been largely studied for the treatment of endometriosis-associated pain and their mechanism of action consists in inhibiting the synthesis of prostaglandins at both the COX-1 and COX-2 sites (90).

Parecoxib, a selective COX-2 inhibitor, has been investigated for treating endometriosis in a rat model, showing to reduce size and microvessel density of implants, and also the expression of VEGF, Flk-1 and PG-E₂ (91). Promising findings were also observed with celecoxib that was able to induce apoptosis in cultures of endometrial epithelial and stromal cells (92, 93) and to decrease number and size of peritoneal implants in mouse model (94-96).

TNF- α is an inflammatory cytokine responsible for the activation of transcription factors involved in inflammation. It has also an important role in the proliferation ectopic and eutopic endometrial cells, and in facilitating cell adherence in implants (97, 98). Two human recombinant TNF- α antagonists, TNFRSF1A and c5N, showed to exert inhibitory effect on endometriotic lesions without affecting the menstrual cycle in baboons (99, 100). Moreover, etanercept, a fusion protein consisting of human recombinant soluble TNF receptor 2 conjugated to a human Fc antibody

subunit, was efficacious in reducing the volume and histopathologic scores of rat's implants, decreasing also serum levels of VEGF, IL-6, and TNF- α (101-103).

Furthermore, infliximab, a monoclonal antibody directed against TNF- α was efficacious in decreasing the size of endometriotic lesions and the plasma levels of nitric oxide (NO) and in increasing the plasma levels of asymmetric dimethylarginine (ADMA) in the rats with endometriosis (104). These observations paved the way to a randomized placebo-controlled trial including 21 women with severe pain due to rectovaginal endometriosis of at least 1 cm in diameter. Differently from previous studies, infliximab did not modify size or number of endometriotic implants and did not improved pain associated to DIE (105).

p38 mitogen-activated protein kinase (p38 MAPK) is an intracellular signal-transducing molecule that causes pro-inflammatory cytokines expression, leukocyte adhesion and chemotaxis of inflammatory cells (106, 107). Several studies suggest its contribute in the pathogenesis of endometriosis (108-110). In mice, FR 167653 and SB203580, two p38 MAPK inhibitors, succeeded in suppressing peritoneal inflammation, and in decreasing the weight and size of the endometriotic implants. Moreover, these drugs significantly reduced the levels of IL-1 β , TNF- α , MMP-2 and MMP-9 in peritoneal fluid and cells (111, 112).

AKR1C3 is a gene that encodes a member of the aldo/keto reductase superfamily. This enzyme catalyzes the reduction of several PGs, such as PG-D2, PG-H2 and the oxidation of 9- α ,11- β -PG-F2 (113). An ongoing randomized, placebo-controlled, double-blind, dose-response study is assessing the efficacy and safety of different oral doses of BAY1128688 in women with symptomatic endometriosis over a 12-week treatment period (NCT03373422).

7.0 Immunomodulation

Nuclear factor (NF)- κ B family includes a group of transcription factors significantly involved in the inflammatory and immune processes. It has a fundamental role in development and establishment of endometriotic implants (114). Several inhibitors of NF- κ B, such as I κ B protease inhibitor

(TPCK), thalidomide, BAY 11-7085, the urinary preparation human chorionic gonadotropin A (hCG-A), pyrrolidinedithiocarbamate (PDTC), and costunolide, have been tested *in vitro* and on animals for the treatment of endometriosis. All these studies showed a reduction of the expression of genes that regulate the production of inflammatory cytokines, extracellular matrix metalloproteinases (MMPs), apoptosis inhibitors, and VEGF (115-121).

Among natural immunomodulators, curcumin is a polyphenolic molecule derived from *Curcuma longa* that it is able to inhibit NF- κ B and induce a p53-mediated apoptosis (122). This drug modulates also VEGF and MMP-3 expression and decreases the production of inflammatory molecules, such as IL-6, IL-8, MIF, MCP-1, ICAM-1, and VCAM-1 in cultures of human ectopic endometriotic stromal cells (123-125). *In vivo* curcumin demonstrated to decrease the size of endometriosis implants (126). Specifically, the effect on the apoptotic pathway of curcumin was studied in mice in comparison with celecoxib. Curcumin increased the Bax/Bcl-2 ratio, the expression of p53, and the apoptotic index of stromal and epithelial endometriotic cells significantly more than the COX-2 inhibitor (125). Recently, it was shown that the combination of curcumin and deferoxamine, an iron-chelating agent, reduces implant size and cell proliferation in rats with endometriosis (127).

DLBS1442 is a bioactive fraction extracted from the fruit of the native Indonesian plant, which has immunomodulatory and anti-inflammatory activities as well as antiangiogenic and apoptosis-inducing effects. In mice model, DLBS1442 showed to inhibit angiogenesis and cell migration in a dose-dependent manner. Regarding its mechanism of action, it targeted the eicosanoid signaling pathway by reducing the NF κ B transcription level and inducible nitric oxide synthase (128). After being investigated in a clinical trial to treat dysmenorrhea (129), an ongoing prospective, randomized, double-blind controlled study is testing its efficacy for the treatment of pain in patients with suspected endometriosis (NCT01942122).

A randomized, placebo-controlled, single blind, experimental study assessed the efficacy of imiquimod, an imidazoquinoline which induces monocytes, macrophages, and dendritic cells to produce cytokines, in experimental endometriosis on rats. The intraperitoneal administration of

imiquimod significantly reduced the volume of endometriotic lesions compared to controls (130). A recent study evaluated an inhibitor of c-Jun N-terminal kinase, bentamapimod (AS602801), which acts on multiple immune pathways, in animal endometriosis model. AS602801 caused regression of 48% of lesions, causing a decrease of inflammatory cytokines. In addition, it enhanced natural killer cell activity, without exerting apparent negative effects on uterus (131).

Recently, V-Endo, a tableted preparation derived from hydrolyzed, heat-inactivated, pooled blood of women with endometriosis has been introduced. When taken orally it is postulated to cause the immune tolerance and anti-inflammatory effect as a result. An ongoing single-arm I-II trial in recruiting patients for testing it. The primary outcome is its efficacy in treating pelvic pain (NCT03340324).

7.0 Antioxidants agents

Oxidative stress has been demonstrated to contribute in the development and progression of endometriosis. In fact, the increased production of inflammatory mediators such as cytokines, reactive oxygen species and prostaglandins (PGs) characterizes endometriotic implants (132). Thus, a large variety of antioxidants have been tested in vitro (133).

Statins, competitive inhibitors of the 3-hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase, exert intrinsic antioxidant activity and exhibit anti-proliferative and anti-angiogenic activity at high doses (134). In a pre-clinical study conducted on mice, endostatin, a proteolytic fragment of collagen XVIII, suppressed the growth of endometriotic implants by 47% compared with controls (135). Simvastatin, another largely used statin, significantly inhibited the proliferation of endometriotic stromal cells, reducing their adhesion to collagen fibers (136). In nude mice, the administration of simvastatin (5 or 25 mg/kg/day) for 10 days caused a dose-dependent reduction of the number and size of endometrial implants by decreasing MMP-3 expression. At the highest dose, the number and the volume of endometrial implants was decreased by 87% and by 98%, respectively (137).

In two preclinical studies on rats, atorvastatin was effective in inducing regression of endometriotic implants. In a prospective randomized-controlled study, animals receiving atorvastatin at high-dose (2.5 mg/kg) had a significant decrease of implants areas and of VEGF levels of peritoneal fluid (138). In the other study, its administration caused a decrease of VEGF and MMP-9 expressions and an increase of MMP-2 tissue inhibitor expression (139).

Metformin has anti-inflammatory activity and is able to modulate the ovarian steroid production. In a pre-clinical study on animal, Yilmaz *et al.* showed that metformin decreases the size and the number of endometriotic lesions by enhancing the levels of superoxide dismutase, and MMP-2 tissue inhibitor, and by reducing levels of VEGF and MMP-9 (140).

Thiazolidinediones target with a high affinity peroxisome proliferator-activated- γ (PPAR- γ) receptors which are involved in cell growth, angiogenesis and has anti-inflammatory activity (141). In the animal model, the treatment with tosiglitazone, ciglitazone or pioglitazone succeeded in inhibiting proliferation and in augmenting apoptosis of endometriotic cells. Moreover, these drugs reduced growth and caused regression of established implants when compared with controls (96, 141-143).

Among vitamins, elocalcitol (in miglyol orally, once a day, 5 days a week), a vitamin D receptor agonist with low calcemic liability, was able to decrease total lesion weight up to 70% after two weeks of treatment in mice with experimental endometriosis. Exploring its mechanism of action, it was demonstrated that elocalcitol reduced cell adherence to collagen, the recruitment of macrophage and the secretion of inflammatory cytokines in the peritoneum of the treated animals (144).

A peculiar gene expression pattern has demonstrated a decrease in uptake and metabolism of vitamin A, a molecule with immune-modulatory and anti-inflammatory proprieties, in women with endometriosis. More, its alteration may provide a partial explanation to the resistance to apoptosis of endometriotic cells (145, 146). In mice with induce endometriosis, the 17-day administration of retinoic acid decreased the number of endometriotic lesions in comparison to a control group.

Moreover, mice receiving the vitamin A had a lower peritoneal IL-6 and MCP-1 concentrations, and a higher expression of CD38, CD11b, and F4/80 on macrophages (147). In another pre-clinical study, this drug confirmed to reduce the volume of established endometriotic implants (75).

In vitro, omega-3 fatty acids inhibit the release of inflammatory mediators in endometrial stromal cells (148). A prospective, randomized experimental study evaluated the anti-inflammatory effect of n-3 eicosapentaenoic acid in comparison with n-6 linoleic acid in the experimental rat model of endometriosis. The mRNA of MMPs, IL-1 β , IL-1 receptor, prostaglandin E synthase and NF-kB expressions were decreased more in the group receiving the omega-3 fatty acids (149). Another study demonstrated that both endogenous and exogenous eicosapentaenoic acid-derived polyunsaturated fats protect against the development of implants through their anti-inflammatory effects. In particular, the 12/15-12/15-lipoxygenase-pathway metabolites of eicosapentaenoic acid seem to be important mediators to suppress the progression of implants (150). A further study in rat showed that omega-3 polyunsaturated fatty acids induced lesions regression more than 1,25-dihydroxyvitamin-D3 (151). A cohort of women with endometriosis was treated for three months with a combination of antioxidants, including omega -3 and- 6 fatty acids. The authors showed a significant reduction of the symptoms as well as in PGE₂ and CA-125 serum levels of patients treated with the dietary composition than controls (152).

N-acetylcysteine is an antioxidant that downregulates inflammatory protein production and gene expression (148). In an observational cohort study, women with endometriosis received N-acetylcysteine (600 mg three times a day, 3 consecutive days a week) for 3 months. After 3 months, the administration of N-acetylcysteine showed that OEs diameter were slightly reduced (-1.5 mm) in comparison with a significant increase (+6.6 mm) in the untreated patients (153).

The antioxidant and anti-inflammatory effects of α -lipoic acid was studied in a controlled experimental endometriosis-induced rat model by evaluating biochemical and histopathologic parameters. The serum total oxidant status and oxidant stress index levels, the endometrial implant

volumes, the serum and peritoneal TNF- α concentrations, and the histopathologic scores were significantly lower in the experimental group (154).

Resveratrol is a phytoalexin derived from grapes with potential antioxidant activity. Its anti-inflammatory effect of resveratrol is mediated by several mechanisms including the inhibition of (NF)-kB activation. In animal models of endometriosis, the supplementation of resveratrol displayed to decrease the number and volume of endometrial implants, suppressing inflammation and decreasing cell proliferation and survival of ectopic endometriotic cells (155). In a small open-label clinical trial, 12 women with endometriosis who failed to obtain pain relief during COC use (drospirinone 3 mg and EE 30 μ g) received the addition of resveratrol (30 mg/day). The patients had a significant reduction in pain scores, with 82% of them reporting complete resolution of dysmenorrhea and pelvic pain after 2 months of therapy (156). Recently, these results have not been confirmed by another study in which resveratrol (40 mg/day, 22 patients) was evaluate in comparison with monophasic COC (levonorgestrel 0.15 mg/EE 0.03 mg, 22 patients, showing no in the two groups regarding pain scores at VAS (157).

8.0 Epigenetic inhibitors

Epigenetic inhibitors are an early investigated target in endometriosis (158). They target histone deacetylases, a family of enzymes that control the acetylation status of histones, modulating cell survival and proliferation (159). It was also demonstrated that histone deacetylases are involved in controlling the expression of steroid hormone-related genes (160), justifying their investigation in endometriosis. In a pre-clinical study, trichostatin A exerted antiproliferative activity against endometrial stromal cells with more potent and longer lasting effect than other drugs, such as SPRMs and N-acetylcysteine. In particular, it induced cell cycle arrest by blocking COX-2 (161, 162). In another pre-clinical study, Lu *et al.* observed that its use significantly decreased the size of implants, as well as improved the response to noxious thermal stimulus (163). Moreover, valproic

acid, another potent histone deacetylase inhibitor, was effective in decreasing the size of endometriotic implants and was well tolerated in rats treated (164).

9. Conclusion

Almost all currently available treatments of endometriosis are suppressive and not curative. For this reason, research is focalized on finding new therapeutic options. Several investigational drugs targeting specific pathophysiological mechanisms involved in endometriosis development, such as inflammation, neoangiogenesis, or apoptosis, are being investigated in early and late clinical trials for the treatment of endometriosis. However, most of them have been tested just *in vitro* or in animals and their clinical use in women is far to be applicable.

10. Expert opinion

The development, maintenance and progression of endometriosis is due to a variety of altered mechanisms including cell proliferation, immune function, apoptosis, invasion capacity and angiogenesis. The growing knowledge of different molecular pathways involved in endometriosis development paved the way for the investigation of new drugs.

Patients with endometriosis require a chronic therapy and, therefore, when choosing the best treatment efficacy in improving pain should be balanced with cost and a good safety-profile (9). If COCs have been used for decades as the first-line treatment for symptomatic endometriosis, progestins are increasingly and successfully employed as monotherapy. Currently, it controversial whether COCs should be preferred or not to progestins as monotherapy (165, 166). In fact, it has been supposed that COCs, causing a supraphysiological levels of estrogen, may be theoretically responsible of an estrogen dominance in presence of progesterone resistance, leading to an eventual progression of endometriosis under therapy (165). Anyway, more studies are needed to draw conclusion on this topic.

Anyway, almost all currently available treatments of endometriosis are suppressive and not curative. In fact, they are associated with the temporary relief of symptoms during treatment, but at its discontinuation, the recurrence of symptoms is common. Moreover, current treatment options for endometriosis-associated pain, excepting NSAIDs, are contraceptive. Thus, these therapies are not suitable for patients wishing to become pregnant.

Overall, medical therapy with progestins enables satisfactory long-term pain control in around two-thirds of symptomatic women. For patients refractory to traditional first-line therapies the administration of GnRH-as is suitable, but is associated to a less favorable profile of tolerability. Thus, new alternative treatment options are demanding.

Over the last 20 years research has focused on developing drugs targeting specific critical pathways of endometriosis (167). Theoretically, these compounds should act on the hormonal and immunological environment of endometriotic implants, downregulating cell proliferation and enhancing apoptosis, re-normalizing their invasive mechanisms and upregulated adhesion or inhibiting angiogenesis.

The most investigated agents are GnRH-ant and AIs. After promising findings from phase II studies, Elaris Endometriosis I-II trials (25) showed that both higher and lower doses of elagolix were effective in improving dysmenorrhea and chronic pelvic pain during a 6-month period in women with endometriosis-associated pain. However, the treatment with two doses of elagolix were associated with higher hypoestrogenic AEs. Currently, ongoing phase III trials have to confirm its efficacy (NCT03343067 and NCT03213457). Anyway, the data available suggest that elagolix at 150 mg once daily may have the potential for longer-term use for the management of endometriosis-associated pain, without the need for add-back therapy. Currently, no randomized controlled trials exist yet to compare GnRH-ant with COCs or progestins. Thus, no inferiority studies to compare them with other treatment options are required in the near future.

AIs has shown promising results in terms of endometriosis-related pain improvement, but, their clinical use is strongly limited by the high AE rate. However, the research of alternative delivery

formulation is attractive. Currently, a combination of anastrozole and levonorgestrel in a vaginal ring is under evaluation (NCT02203331) and may represent an intriguing future option.

The use of SERMs and SPRMs to treat endometriosis is unlikely to become a first-line strategy due to the unsatisfying results observed in laboratory/animal studies (48) (103, 168). Furthermore, these compounds share the same receptors and therapeutic mechanisms with the existing agents, including the potential contraceptive effect.

Several antiangiogenic agents have been tested in animal models, showing efficacy in reducing the establishment and maintenance of endometriotic implants. However, the role of inhibiting angiogenesis in humans with endometriotic lesions present for years at the time of diagnosis remains unclear. Furthermore, owing to their severe AEs related to interference with physiologic angiogenesis, their translation into human research has been limited (169-171). A small proof-of-concept study demonstrated promising findings in terms of efficacy and safety with the use of quinagolide, a dopamine agonist, to treat patients with peritoneal endometriosis (89); however, these preliminary results have to be confirmed in larger, well-designed trials.

Among anti-inflammatory drugs, TNF- α blockers have shown good efficacy in animal studies. In particular, etanercept is currently administered with a good safety profile in the treatment of chronic inflammatory diseases in humans, but no trials in women with endometriosis has been performed. On the other hand, the promising results of infliximab in pre-clinical study have not been confirmed in a small clinical trial on women (168).

Oxidative stress may participate to the development and progression of endometriosis, and, thus, it may be a suitable target for the treatment of endometriosis (132). The efficacy of several antioxidants to relieve endometriosis-associated pain and to reduce endometriotic lesions has been assessed, but only poor evidence exists to support their clinical application. In particular, it appears rational the investigation of statins, metformin and thiazolidinediones, because they exert antioxidant and anti-angiogenic activities, they are not expensive and are largely available. After having been tested

successfully in animal with endometriosis, large further studies in vivo are needed to draw conclusion on their efficacy in women with endometriosis.

In addition, as aberrant methylation of the progesterone receptor gene seems to take part in the process of specific gene silencing in endometriosis (158), demethylation agents and histone deacetylase inhibitors have been proposed as alternative possible options. It seems promising the use of valproic acid in animals because of its efficacy and its safety-profile. Although the interesting results from a cases series of women with adenomyosis treated with valproic acid (172), no trials on its use for endometriosis exist, thus, any beneficial effect of this drug has to be confirmed (173).

In conclusion, a great number of investigational drugs targeting many pathogenic mechanisms have been proposed for the treatment of endometriosis. However, the majority of these agents have been investigated only in experimental and preclinical models and more extensive researches are mandatory to address their efficacy and safety profiles in women.

It is important to under light that current rodent models of endometriosis have some limitations: at first the endometriotic disease is experimentally induced, requiring excision of uterine horn endometrium and suturing of the implants into the peritoneal surface in the presence of E₂ at high doses. In fact, this manipulation is required since rodents have an estrous cycle; it is rather controversial whether this procedure recapitulates accurately the pathophysiology of endometriosis. The only animal models that appear to be highly reproductive of human endometriosis are primate models in which a menstrual cycle is present. Anyway, these animals are rarely used in these pre-clinical trials for high cost and ethical concerns. Secondly, the experimental endometriotic implants are often surgically induced only in peritoneum, and not in other localizations. It appears unlikely that investigational drugs may have the same efficacy in treating peritoneal lesions, OEs and, more importantly, large implants of DIE, which have an high content of fibromuscular tissue, and may have already been present for some years (171). Another important consideration is that the modification of size and number of implanted endometrium fragments are typically the main

outcome on studies on animal model whereas the more important outcome of human research for endometriosis today is generally symptomatic relief (174).

In our opinion, only a minority of these tested drugs may be considered for future studies, as the safety profile of these agents is the turning point for their use in the treatment of a chronic benign disease. Thus, in the absence of solid clinical data deriving from large randomized controlled trials, the introduction of new targeted drugs for endometriosis is far to be realized. More clinical trials are mandatory before these therapies may be considered for the treatment of patients with endometriosis.

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Tables

Table 1. Investigated drugs for the treatment of endometriosis

	Class	Drugs	Most advanced study
Hormonal treatment	GnRH antagonist	Cetrorelix ⁽¹⁾ , elagolix ⁽²⁾	III ^(1,2)
	Aromatase inhibitors	Anastrozole ⁽¹⁾ , letrozole ⁽²⁾	III ^(1,2)
	SERM	Bezedoxifene ⁽¹⁾ , raloxifene ⁽²⁾	II ^(1,2)
	SPRM	Mifepristone ⁽¹⁾ , anoprisnil ⁽²⁾	II ^(1,2)
Anti-angiogenic drugs	Anti-VEGF	Bevacizumab ⁽¹⁾	Animal model ⁽¹⁾
	TKIs	Sunitib ⁽¹⁾ , Sorafenib ⁽²⁾ , Pazopanib ⁽³⁾	Animal model ^(1,2,3)
	mTOR	Rapamycin ⁽¹⁾ , Temsirolimus ⁽²⁾ , Everolimus ⁽³⁾	Animal model ^(1,2,3)
	Dopamine agonists	Cabergoline ⁽¹⁾ , quinagolide ⁽²⁾	II ^(1,2)
	Others	TNP-470 ⁽¹⁾	Animal model ⁽¹⁾
	Anti-inflammatory	COX-2 inhibitors	Parecoxib ⁽¹⁾ , celecoxib ⁽²⁾
Anti TNF-α		Etanercept ⁽¹⁾ , infliximab ⁽²⁾ ,	Animal model ^(1,3,4) ,

		TNFRSF1A ⁽³⁾ and c5N ⁽⁴⁾	phase II ⁽²⁾
	MAPK inhibitors	SB203580 ⁽¹⁾ , FR167653 ⁽²⁾	Animal model ^(1,2)
Immunomodulators	NfKb inhibitors	IκB protease inhibitor (TPCK) ⁽¹⁾ , BAY 11-7085 ⁽²⁾ , urinary preparation of human chorionic gonadotropin A (hCG-A) ⁽³⁾ , pyrrolidinedithiocarbamate (PDTTC) ⁽⁴⁾ , costunolide ⁽⁵⁾ , curcumin ⁽⁶⁾ ,	Animal model ^(1,2,3,4,5,6) , I-II ⁽⁷⁾
	Others	DLBS1442 ⁽¹⁾ , imiquimod ⁽²⁾ , bentamapimod ⁽³⁾ , V-endo ⁽⁴⁾	Animal model ^(1,2,3) , I-II ⁽⁴⁾
Antioxidants drugs	Statins	Endostatin ⁽¹⁾ , simvastatin ⁽²⁾ , atorvastatin ⁽³⁾ , rosuvastatin ⁽⁴⁾	Animal model ^(1,2,3,4)
	Antidiabetic drugs	Metformin ⁽¹⁾ , ciglitazone ⁽²⁾ , pioglitazone ⁽³⁾ , rosiglitazone ⁽⁴⁾	Animal model ^(1,2,3,4)
	Vitamins	Elocalcitol (Vit D) ⁽¹⁾ , retinoic acid (Vit A)	Animal model ^(1,2)
	Other antioxidants	Omega-3 fatty acids ⁽¹⁾ , N-acetylcysteine ⁽²⁾ , α-lipoic	Animal model ^(1,3) , II ⁽²⁾

		acid ⁽³⁾	
Epigenetic drugs	Histone deacetylase inhibitors	Trichostatin A ⁽¹⁾ , valproic acid ⁽²⁾	Animal model ^(1,2)

GnRH=gonadotropin releasing hormone, SERM=selective estrogens receptor modulator;
 SPRM=selective progesterone receptor modulator; NFkB= nuclear factor kappa-light-chain-
 enhancer of activated B cells, VEGF=vascular endothelial growth factor, TKI=tyrosine kinases
 inhibitors, MAPK=Mitogen-activated protein kinase

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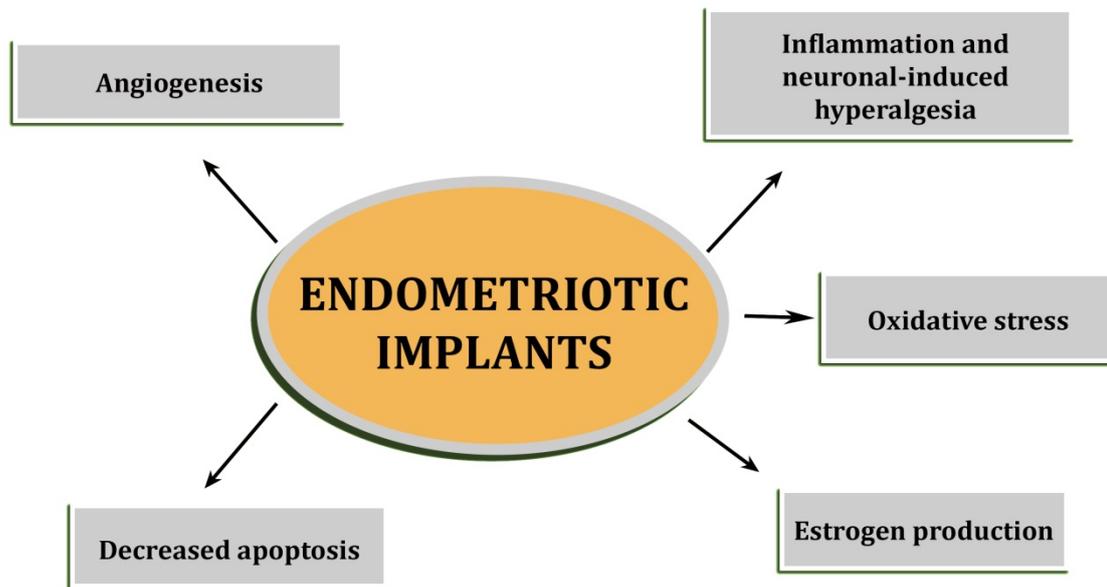


Figure 1. The pathogenesis of endometriosis involved several factors. The improvement of the knowledge of principal pathways altered in this benign chronic disease is leading to the development of new specific targeted drugs.

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