New trends for the medical treatment of endometriosis

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Introduction: Endometriosis is a benign sex hormone-dependent gynecological disease, characterized by the presence and growth of endometrial tissue outside the uterus; it affects 10% of women of reproductive age and is associated with infertility and pain. Treatment of endometriosis involves conservative or radical surgery, or medical therapies. The goals for endometriosis treatment may be the relief of pain and/or a successful pregnancy achievement in infertile patients. Treatment must be individualized with a multidisciplinary approach. The classical treatments carry adverse side effects and in some cases a negative impact on quality of life. New agents promise a distinct perspective in endometriosis treatment.

Areas covered: The aim of this paper is to systematically review the literature evidence of new medical treatments for endometriosis, defined as pharmacological treatments not yet commonly available and currently under investigation.

Expert opinion: These new medical therapies would be used associated with surgical treatment and, in the future, will render possible the association of hormone therapy with non-hormonal treatment for endometriosis.

Keywords: acupuncture, antiangiogenic therapy, antioxidant therapy, endometriosis, natural extracts, new treatment, omega-3, selective estrogen receptor modulator, statins, thiazolidinedione, vitamins

1. Introduction

Endometriosis is a benign sex hormone-dependent gynecological disease, characterized by the presence and growth of endometrial tissue outside the uterus; it affects 10% of women of reproductive age and is associated with infertility and pain [1,2]. The disease can be manifested by three clinically distinct forms: pelvic endometriotic implants, ovarian endometriomas and deep endometriotic nodules [1,2]. The pain may be manifested by dysmenorrhea, dyspareunia or chronic pelvic pain [3]. Deep endometriosis may affect the bladder and rectum, causing dyschezia, dysuria and hematochezia [4]. The symptoms can impact on general physical, mental and social well-being [5].

Despite extensive research, the understanding of the pathogenesis of endometriosis remains incomplete [5]. The disease derives from retrograde menstruation of endometrial cells which implant on peritoneal surfaces and induce an inflammatory response. The success of the ectopic implants depends on other pathological processes such as angiogenesis, adhesions, fibrosis, immune dysfunction and neuronal infiltration [1,2,6-8].

The treatment of endometriosis involves conservative or radical surgery, or medical therapies. The goals for the endometriosis treatment may be the relief of pain and/or a successful pregnancy achievement in infertile patients. Women with endometriosis (WEN) may require chronic therapy and, therefore, efficacy should

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be balanced with adverse effects on the choice of the best treatment option. Treatment must be individualized with a multidisciplinary approach.

1.1 Surgery
Surgical approaches to relieve endometriosis-related pain include laparoscopy with fulguration, ablation and excision of lesions, and are used as first-line therapy or initiated after failed medical therapies [1,5]. Surgical therapy is specially indicated in patients with pelvic pain, without relief of pain with medical therapy and in patients with deep infiltrating endometriosis [1,5]. Laparoscopic cystectomy could be the treatment of choice for ovarian endometriomas larger than 4 cm diameter, and probably improves fertility compared with drainage and coagulation [9-11]. However, ultimate best treatment has yet to be discovered regarding fertility and endometriomas. Ablation of endometriotic lesions with lysis of adhesions improves fertility in minimal-mild endometriosis [1,5]. Symptomatic deep infiltrating endometriosis lesions should be completely resected during a one-step surgical procedure; the multifocality of deep endometriosis lesions requires several associated surgical procedures [3,5,10,12]. In deep endometriosis, the complete surgery provides good long-term functional results when all endometriotic lesions are resected during the same surgical procedure [12]. With laparoscopy, anesthesia, infection, damage to internal organs, new adhesions and hemorrhage are associated risks [1].

1.2 Current medical treatment
The strategy of medical treatment for endometriosis is based on blocking ovarian function, creating a state of iatrogenic menopause or pseudopregnancy (Figure 1). To obtain such effects, hormones are the main drugs used. These include progestins, oral contraceptives and gonadotropin-releasing hormone (GnRH) analogs. Hormone drugs are recognized as first-line treatment to reduce symptoms of pain in patients without surgical indication or when there is a contraindication to surgery, and to prevent recurrence of disease after surgery [13-16]. The empirical treatment of pain symptoms suggestive of endometriosis can be utilized without a definitive diagnosis, using a hormonal agent [1,5]. Non-steroidal anti-inflammatory drugs (NSAIDs) are effective in reducing pain associated with endometriosis by reducing the secretion of prostaglandins and other inflammatory substances [17,18].

The classical treatments carry adverse side effects, including vasomotor symptoms, suppression of reproductive function and in some cases a negative impact on quality of life. To prevent the unnecessary side effects of classical medical treatment options, new agents promise a distinct perspective in endometriosis treatment (Table 1). Some of these new drugs act on reducing estrogenic activity (GnRH antagonist, aromatase inhibitors (AIs), selective estrogen receptor modulators (SERMs)), or causing a pseudopregnancy (progestins, selective progesterone receptor modulators (SPRMs)) or more downstream in the pathogenetic cascade (anti-inflammatory, antiangiogenic, proapoptotic).

The aim of this paper is to systematically review the literature evidence of new medical treatments for endometriosis, defined as pharmacological treatments not yet commonly available and currently under investigation.

2. Methods

2.1 Search strategy
A systematic literature search was performed to identify new medical treatments to endometriosis. Articles were identified through the following electronic databases: MEDLINE (until November 2011) and the Cochrane Central Register of Controlled Trials (The Cochrane Library until July 2011). The following combinations of Medical Subject Headings (MeSH) and text words were used to generate the list of citations: (endometriosis OR pelvic pain) AND (new treatment OR novel treatment OR vitamins OR statins OR omega-3 OR selective estrogen receptor modulator OR natural extracts OR botanical extracts OR vitamin C OR antioxidant therapy OR progesterone antagonist OR acupuncture OR thiazolinedione OR antiangiogenic factor OR antiangiogenic therapy OR SERM OR antioxidant therapy OR cannabinoid agonists).

All relevant articles were examined and their reference lists were systematically reviewed in order to identify other studies for potential inclusion in this systematic review. No institutional review board approval was required because only published data were analyzed.

2.2 Selection criteria
Randomized controlled trials (RCTs), patient preference trials, observational studies, case reports and proceedings of scientific meetings were included in this review, whereas abstracts were excluded. Only publications in English were considered in the selection. The studies included in
the current review were selected according to the following criteria:

- Population: Patients with diagnosis of endometriosis in reproductive age complaining of pain symptoms such as dysmenorrhea, deep dyspareunia, chronic pelvic pain and infertility. Experimental models of endometriosis (mouse, rat, baboon) and in vitro studies (cultured endometrial stromal cells).
- Interventions: New trends for the medical treatment of endometriosis (pain and/or infertility) either alone or in combination with other classical therapies.
- Comparisons: Whenever possible the new treatments should be compared with existing standard treatments such as combined oral contraceptives or progestins; if this was not available, the new treatments were evaluated in comparison with placebo or with no intervention.
- Outcome: Relief in the intensity of endometriosis-related pain symptoms, improvement of fertility, decrease of lesion size, proapoptotic effects, decrease in angiogenesis.

The abstracts retrieved were reviewed by two authors (ALLR and FMR) to exclude irrelevant citations. The reviewers worked independently. Any disagreement between the two reviewers was resolved by consensus or determination by a third reviewer (FP). The reviewers were not blinded to the names of investigators or sources of publication.

3. Hormonal drugs

3.1 Gonadotropin-releasing hormone antagonist
GnRH induces both follicle-stimulating hormone (FSH) and luteinizing hormone (LH) secretion by the pituitary gonadotrope cells. GnRH antagonists induce competitive receptor occupancy of GnRH receptor, leading to a rapid and reversible suppression of gonadotropin secretion [19]. These drugs are effective in suppressing endometriosis-associated pelvic pain when treatment is continued for 3 – 6 months [5]; although combined oral contraceptive, danazol, gestrinone, medroxyprogesterone acetate and GnRH agonists are equally effective, their side effects and cost profiles greatly differ [5]. Treatment with a GnRH antagonist is likely to be just as
3.2 Aromatase inhibitors

AIs have the ability to reduce estrogen production through inhibition of aromatase P450, a key enzyme that catalyzes conversion of androstendionone and testosterone to estrone and estradiol [23]. Aromatase P450 is overexpressed in both eutopic and ectopic endometrium of patients with endometriosis [24-31]. The majority of studies evaluating the use of AIs in endometriosis have focused on relief of pelvic pain and/or effect on endometriotic implant size. AIs combined with progestogens, oral contraceptive pill or GnRH analog reduce the intensity of pain symptoms caused by endometriosis [31-38] and improves quality of life [24]. Letrozole and norethisterone acetate were more effective in reducing pain and deep dyspareunia than norethisterone acetate alone [39]. The administration of AIs seems to reduce the risk of recurrence of pain after the operative treatment [39,40]. In a randomized trial, the combination of AI and GnRH analog was more effective to reduce pain than GnRH analog alone [40]. This therapy does not cause disappearance of endometriotic lesion during treatment and does not prevent recurrence of symptoms after interruption of therapy.

As regards infertility treatment, a non-controlled, pilot study suggested that the combination of anastrazole and goserelin for pituitary down-regulation may reduce the volume of endometriomas before in vitro fertilization (IVF)/intracytoplasmic sperm injection (ICSI) [41]. Some studies have demonstrated that AIs are not able to block completely the ovary, suggesting that their use should be done with other therapies together [42]. However, these drugs have adverse effects such as arthralgia, myalgia and a decrease of bone mineral density, which reduces patient compliance in the long-term treatment [31]. Future studies should be done to clarify if the long-term administration of AIs is superior to currently available medical therapies in terms of pain relief, adverse effects and patient satisfaction.

3.3 Selective estrogen receptor modulators

SERMs directly bind to estrogen receptor (ER)-α and/or ER-β in target cells and exert estrogen- or antiestrogen-like actions in various tissues. SERMs may have tissue-selective effects, acting as ER agonists in the bone, but as ER antagonists in the breast and uterus [43]. A recent study showed that the SERM bazedoxifene antagonizes estrogen-induced uterine endometrial stimulation in a mice model of endometriosis [44]. Bazedoxifene may be an effective new candidate for the treatment of endometriosis because of its endometrial-specific estrogen antagonism compared with other SERMs [44]. Another new SERM, TZE-5323, reduced the size of endometriotic implants in a rat experimental model without decreasing bone mineral density [45]. Raloxifene induced significant implant regression in two studies in rat endometriosis model [46-48]. On the other hand, raloxifene was associated with return of pain earlier than placebo in a RCT in patients with endometriosis [49]. Moreover, the patients treated with raloxifene underwent a second surgery sooner than patients treated with placebo [49].
More studies are necessary to evaluate the use of SERMs as a new treatment of endometriosis. It must be emphasized that the majority of findings were obtained in animal models and that randomized clinical studies are essential before some SERMs can be used as alternatives drugs in the treatment of endometriosis. These drugs can also be associated with an increased incidence of venous thromboembolic events, vasomotor symptoms and sometimes stroke [50], reinforcing the need of safety studies before their introduction to the endometriosis therapeutic arsenal.

3.4 Selective progesterone receptor modulators
SPRMs are new progesterone receptor ligands that exhibit agonist/antagonist effects based on the target tissue [51-53]. SPRMs induce amenorrhea through selective inhibition of endometrial proliferation without the systemic effects of estrogen deprivation [51-54]. Additionally, they suppress endometrial prostaglandin production, providing relief of endometriosis-related pain [54]. SPRMs have an antiproliferative effect because SPRMs binds minimally to ER [51]. Mifepristone is a SPRM that shows a number of pharmacodynamic properties in the human, which may not be induced by its progesterone receptor-agonistic activity, but by discrete progesterone receptor-antagonistic activity [51,52]. Mifepristone and other SPRMs antagonize estrogen effects in the endometrium in primates [55-57], induce endometrial atrophy and amenorrhea in ovariectomized, estrogen-substituted monkeys [52,55-57] and decrease the size of endometriotic implants in a primate model [58]. Large randomized clinical trials on the use of mifepristone in endometriosis must be performed prior to indicating its use in the treatment of this disease. Mifepristone has antiglucocorticoid properties and its long-term safety should be studied more [51-53].

Asoprisnil is a steroidal SPRM in late-stage clinical development that exhibits partial agonist and antagonist activities in vivo [59]. Asoprisnil suppresses endometrial proliferation and induces amenorrhea by targeting the endometrium in non-human primates [54,59]. Moreover, asoprisnil may suppress pain associated with endometriosis through an endometrial-specific mechanism [54,59] and reduced the dysmenorrhea from endometriosis in comparison with placebo in randomized placebo-controlled studies [60,61]. Asoprisnil seems to be safe and well tolerated, but more studies are necessary prior to include this class of drugs as a novel treatment for endometriosis.

4. Non-hormonal drugs

4.1 Cyclooxygenase-2 inhibitor
Cyclooxygenase (COX) is the rate-limiting enzyme in the metabolic conversion of arachidonic acid to prostaglandins, including prostaglandin E2, a major mediator of inflammation and angiogenesis. COX-2 is the inducible form of COX [62]. Endometriotic lesions demonstrated increased expression of COX-2 [63]. Non-selective NSAIDs have been largely studied for the treatment of endometriosis-associated pain and their major action is to inhibit the synthesis of prostaglandins at both the COX-1 and COX-2 sites [64]. NSAIDs may be effective in reducing endometriosis-associated pain [1,5,63,64] but they are associated with various side effects such as gastric ulceration and an anti-inflammatory effect when taken at mid-cycle [5]. Recently, COX-2-specific inhibitors have been studied in the treatment of pain in patients with endometriosis. This group of drugs has high effectiveness with fewer gastrointestinal side effects [65]. Parecoxib, a selective COX-2 inhibitor, decreased the endometriotic implant size, the microvessel density, the expression of VEGF and Flk-1 and the concentration of prostaglandin E2 in a rat model [66]. Another selective COX-2 inhibitor, rofecoxib, used at 25 mg/day, led to a significant relief of both pelvic pain and dyspareunia after 6 months, persisting after the end of the treatment [64]. Rofecoxib also showed higher efficacy and less recurrence of symptoms than placebo, without significant side effects [64]. Celecoxib reduced the mean number of lesions, the cell proliferation within the implants and the implant volume in a mouse model. In addition, apoptosis was enhanced by treatment with celecoxib [67]. Conversely, nimesulide, another COX-2 inhibitor, did not reduce lesion size or number of ectopic endometrial lesions in a nude mouse model of endometriosis. Moreover, nimesulide did not induce difference in blood vessel development or macrophage or myofibroblast infiltration in nude mouse explants [68]. Clinical studies should be performed to test the safety and effectivity of these new drugs in patients with endometriosis.

4.2 Antioxidant agents
4.2.1 Omega-3 fatty acids
Inflammation is part of the normal host response to infection and injury and excess inflammation may lead to acute or chronic diseases like endometriosis. Endometriosis is characterized by increased endometrial production of inflammatory mediators such as cytokines, reactive oxygen species and prostaglandins. Omega-3 fatty acids inhibit the release of inflammatory mediators like IL-8 and prostaglandins in human endometrial stromal cells (HESC) [69]. Eicosapentaeenoic acid (EPA) and docosahexaenoic acid (DHA) reduced IL-8 and prostaglandin E2 secretion and COX-2 mRNA expression in TNF-α-treated HESCs, supporting their effect as anti-inflammatory compounds [69]. Inflammation is the main cause of pelvic pain in patients with dysmenorrhea [70] or endometriosis [71], and TNF-α is a key regulatory factor that stimulates peritoneal endometrial secretion of IL-8 and expression of COX-2, which in turn increases the production of prostaglandin E2, a possible mechanism by which TNF-α causes pain [72]. A possible effect of these fatty acids in endometriosis has also been suggested by evidence that omega-3 fatty acid supplementation decreased prostaglandin E2 concentrations and endometriotic implant diameter in a rabbit model with surgically induced endometriosis [73]. Another study demonstrated that EPA dietary...
supplementation shows beneficial effects, histologically demonstrated by a reduction in the thickness of the interstitium of the endometriotic tissue in a rat model of endometriosis [74]. Moreover, EPA suppresses some of the genes involved in the pathogenesis of endometriosis, like IL-1β, IL-1r2 and IL-10, which were down-regulated after the oral administration of EPA [74-78]. A study reported that dietary supplementation with omega-3 fatty acid has a beneficial effect on symptoms of dysmenorrhea in adolescents [79]. Increased exposure to EPA significantly suppresses the in vitro survival of endometrial cells [80]. In a non-randomized prospective study, patients with endometriosis, after conservative surgery, treated with omega-3 fatty acids (800 mg/day) for 12 months demonstrated improvement of pelvic pain and dyspareunia [81]. These preliminary findings suggested a possible use of omega-3 fatty acids in the management of endometriosis by reducing the inflammatory response and modulating cytokine function.

4.2.2 Statins
Statins are inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase with intrinsic antioxidant activity [82]. The proliferation of endometrial stroma is stimulated by oxidative stress and inhibited by an assortment of antioxidants [83]. Evidence supports the potential use of statins as a new treatment in endometriosis. Lovastatin reduced the proliferation of stromal cells and abolished angiogenesis in an in vitro model of endometriosis [84,85]. Statins inhibit the growth of endometrial stromal cells in a concentration-dependent manner [84]. Moreover, atorvastatin reduced the size of surgically induced experimental endometriosis in a rat autotransplantation model [86]. Additionally, simvastatin induced a dose-dependent reduction in the number and volume of endometriotic implants in a nude mouse model of endometriosis [87]. Statins also inhibit several MMPs, including MMP-3 and MMP-7 [88-90] and this inhibition seems to prevent the development of endometriosis-like lesion in an animal model [91]. The fact that simvastatin induced apoptosis [92] may contribute to inhibition of cell growth and protection from growth of endometrial implants. Statins seem to have anti-inflammatory, antioxidant, antiproliferative and antineoplastic properties in various biological models, making its use an encouraging potential treatment for endometriosis [92-94].

4.2.3 Natural herbs and vitamins
Botanicals seem to have antiproliferative and anti-inflammatory activity on endometrial cells, suppressing endometriotic implants in animal models [94-96]. Chinese herbal mixtures use botanicals in various combinations to treat the symptoms associated with endometriosis [94]. A mixture of nine anti-inflammatory herbs showed an antiproliferative effect, decreasing endometriotic stromal cell proliferation in vitro in a dose-dependent way [97]. Moreover, this herbal mixture induced apoptosis showing a proapoptotic effect and supporting the potential therapeutic use of botanicals in the treatment of endometriosis [97]. Also single components of the herbal mixture suppressed cell proliferation in vitro [95,97]. One randomized study comparing the efficacy of Ywei ning, a medicinal herbal mixture, and gestrinone for post-operative treatment of endometriosis demonstrated that the botanical mixture prevented the post-operative recurrence of endometriosis in an effective and safe manner, and its efficacy was similar to that of gestrinone [98]. Prunella vulgaris, a common Chinese herb, had antiestrogenic activity in in vitro and in vivo models and may be useful as an adjunct for the treatment of estrogen-dependent diseases such endometriosis [99]. Additionally, medicinal herbs demonstrated anti-inflammatory effects in animal models and in WEN [94]. More studies are necessary to better understand the effectiveness and safety of botanicals as a new option to the treatment of endometriosis.

Another natural product that has been studied as a new treatment of endometriosis is resveratrol, a non-flavonoid polyphenolic compound found in grapes and red wine, with anti-inflammatory proprieties. Resveratrol has been shown to suppress the induction of nitric oxide synthase and disrupt arachidonic acid metabolism by inhibiting COX-2 [100,101]. This polyphenol exhibits many biological activities including prevention of oxidative stress and cell proliferation, and induces apoptosis in numerous tumor cells [102-109]. In endometriosis, resveratrol decreased the number and the total volume of endometrial implants in the nude mouse and induced a concentration-dependent reduction of invasiveness of HESC [110]. This natural component shows anti-inflammatory, antioxidant, proapoptotic and antiproliferative activities, being a potential new treatment for endometriosis.

Vitamin E, vitamin C and β-carotene are antioxidants that counteract the effect of free radicals. Oxidative stress arises when there is an excess of free radicals resulting in damage to cells and cell membrane [111]. Oxidative stress probably plays an important role in the development and progression of endometriosis. The presence of oxidative stress increases the growth and adhesion of endometrial cells in the peritoneal cavity, leading to endometriosis [111-115]. Additionally, conditions of higher oxidative stress could disturb several immunological mechanisms [115]. The peritoneal fluid of patients with endometriosis has low concentration of ascorbic acid (vitamin C), an antioxidant, and shows an imbalance in its antioxidant and oxidative markers, promoting an oxidative stress condition [115]. WEN seems to have a lower antioxidant intake when compared with women without endometriosis (WWE) [116]. When WEN were treated with a highly antioxidant diet, there was an increase in the vitamin concentrations and in the antioxidant enzyme activity as well as a decrease in peripheral oxidative stress markers [116,117]. On the other hand, antioxidant dietary therapy, consisting of supplementation of vitamins (B6, A, C, E), mineral salts (Ca, Mg, Se, Zn, Fe), lactic ferments VSL3 (Bifidobacterium breve, Bifidobacterium longum, Bifidobacterium infantis, Lactobacillus
acidiophilos, Lactobacillus casei, Lactobacillus bulgaricus, Streptococcus thermophilus), omega-3 and omega-6 fatty acids after laparoscopic cystectomy had no significant effect on the recurrence rate of ovarian endometriosis when compared with surgery plus placebo [118].

Eocalcitol, a selective vitamin D receptor agonist, reduced endometriotic lesion development and inhibited peritoneal inflammation by decreasing cytokine release and macrophage recruitment in a mouse model [119]. Due to antiproliferative and anti-inflammatory properties of vitamin D and its expression by eutopic and eutopic endometrium, vitamin D could be a potential treatment for endometriosis [120]. Vitamin supplementation could be used as a therapeutic support to improve the balance of antioxidants, contributing to create a peritoneal environment less susceptible to the development of endometriotic implants.

4.2.4 Thiazolidinediones

Thiazolidinediones are a new class of antidiabetic drugs that have been shown to inhibit the expression of various inflammatory molecules in chronic inflammatory diseases and could be used to treat pain associated with endometriosis [121,122]. Rosiglitazone and pioglitazone appertain to this drug class and had anti-inflammatory, antiangiogenic and antioxidant effects in an in vitro study [123]. Rosiglitazone treatment inhibited endometriotic implant growth, cell proliferation and vascularization and augmented apoptosis in experimental endometriosis when compared with controls [67]. Other animal studies sustain the possible use of some thiazolidinediones as a new treatment in endometriosis, since rosiglitazone, ciglitazone or pioglitazone reduced endometriotic growth and caused regression of established implants [123-125], reduced adhesions [126] and the size of experimentally induced endometriotic lesions [117,118] and provoked implant regression in baboons with endometriosis [127,128]. Ciglitazone and pioglitazone reduced IL-6 secretion from endometrial stromal cells [129]. Most of these studies were done on experimental models of endometriosis and further studies are necessary to support the clinical use of thiazolidinediones for the treatment of endometriosis.

4.3 Acupuncture

Several studies have demonstrated the positive effect of acupuncture in the relief of pelvic pain [130-132] and treatment of infertility [133]. Limited evidence from RCTs suggests that acupuncture is effective in treating dysmenorrhea [134-137]. A randomized controlled cross-over trial showed significant reduction of pain with acupuncture as well as an improved quality of life in patients with endometriosis [138]. It is difficult to evaluate the studies on acupuncture in endometriosis because most of them are non-randomized uncontrolled trials, case reports or case series, which are vulnerable to many sources of bias. In addition, there are heterogeneities in the protocols and controls used. Further high quality studies should evaluate the effectiveness of acupuncture in the relief of pain in endometriosis.

4.4 Antiangiogenic agents

Endometriosis is a multifactorial disease in which angiogenesis seems to be involved [139-143]. Some studies have demonstrated that VEGF may be involved in the progress of the ectopic lesions in endometriosis [144,145]. Vascularization, VEGF and its receptor expression are abundant in deeply infiltrating endometriosis, supporting the hypothesis that antiangiogenic therapy might constitute a novel modality of treatment for this disease [143].

Romidepsin, a histone deacetylase inhibitor, inhibited VEGF gene transcription, down-regulated VEGF protein expression and abolished the secretion of VEGF protein in an in vitro study with human immortalized epithelial endometriotic cells [146]. Therefore, romidepsin may be a potential therapeutic candidate against angiogenesis in endometriosis.

Parecoxib, a selective COX-2 inhibitor, decreased the implant size and led to atrophy and regression of endometrial implants in a rat model of peritoneal endometriosis. The treatment with this drug also reduced the microvessel density, the number of macrophages and the expression of VEGF, showing an antiangiogenic effect [66].

Rapamycin, a drug with antifungal, immunosuppressant and antiangiogenic effects, induced regression of endometriotic lesions by inhibiting neovascularization and cell proliferation in an in vitro model [147].

Epigallocatechin gallate (EGCG), the major component of green tea, seems to have antiangiogenic properties and was used on an experimental endometriosis mouse model decreasing endometriotic lesions, glandular epithelium, angiogenesis, microvessel size and density and mRNA expression for VEGF-A in the implants [148]. Moreover, the product from green tea increases apoptosis in endometriotic lesions [148]. Another study confirmed that EGCG suppressed estradiol-stimulated activation, proliferation and VEGF expression in endometrial cells in vitro and inhibited angiogenesis and blood perfusion of endometriotic lesions in vivo, inducing regression of the endometriotic lesions [149]. These antiangiogenic and proapoptotic properties of green tea support its use as a complementary treatment in endometriosis.

Another encouraging drug is bevacizumab, an antiangiogenic agent, which inhibited the development and cell proliferation in endometriotic lesion, reduced vascular density, increased apoptosis and reduced VEGF levels in peritoneal fluid in a murine model of endometriosis [150].

Lodamin is an oral non-toxic formulation of TNP-470, a potent angiogenesis inhibitor. This drug demonstrated a potential clinical use as antiangiogenic therapy for endometriosis, as it suppressed the mobilization of circulating endothelial cells and endothelial progenitor cells and inhibited the growth of endometriotic lesions in a mouse model of endometriosis [151].

Vascular-disrupting agents (VDAs) are promising new drugs for the treatment of tumors. VDAs target established blood vessels and may be more efficient against advanced disease. The encouraging advantage of these drugs is that they seem to note the physiological differences between tumor
and normal endothelium inducing acute vascular shutdown only in the disease. Selective VDAs should be developed prior to be used as a novel therapy for endometriosis [152].

Dopamine and its agonists, such as cabergoline, promote VEGF receptor-2 endocytosis in endothelial cells, preventing VEGF-receptor binding and reducing angiogenesis [153]. Treatment with cabergoline in experimental endometriosis demonstrated an antiangiogenic effect acting through VEGF receptor-2 inactivation [153]. Cabergoline and quinagolide, respectively an ergot and non-ergot-derived dopamine agonists, were able to inhibit neoangiogenesis and endometriotic lesions size in an experimental mouse model of endometriosis [154]. These findings support future studies of dopamine agonists as a new therapeutic approach for endometriosis.

4.5 Cannabinoid agonists

The cannabinoids play a role in the regulation of inflammation and immunological responses [155]. They have antiproliferative effects resulting from the inhibition of growth factors [156,157] and the disruption of growth factor signaling pathways [158-160]. Moreover, cannabinoids showed antifibrotic properties in the liver, pancreatic cells, and fibroblasts in several experimental studies [161-167] and have analgesic properties, relieving chronic pain [168-170]. These properties of cannabinoid agonists could be used for endometriosis treatment since this disease is accompanied by chronic pelvic pain, inflammation, neoangiogenesis and fibrosis. In fact, the effects of WIN 55212-2, a cannabinoid agonist, were evaluated in in vitro and in vivo experiments, demonstrating antiproliferative effects on endometriosis. In vitro, WIN 55212-2 reduced cell proliferation in endometriotic and endometrial stromal cells from women with or without deep infiltrating endometriosis [170]. In vivo, this cannabinoid agonist inhibited the growth of endometriotic tissue implanted in nude mice. More studies are necessary to evaluate the properties and possible clinical use of cannabinoid agonists to treat endometriosis.

5. Expert opinion and conclusion

Endometriosis is a multifactor disease in which estrogens, progesterone and its receptors play an important role in the pathogenesis. Additionally, the development and maintenance of endometriotic implants depend of the regulation of cell proliferation, immune function, apoptosis, invasion capacity and angiogenesis, as summarized in Figure 1.

The current therapeutic options for endometriosis are far from ideal, considering the risks and burdens of surgery, the side effects of GnRH agonists, the limited efficacy of all pharmacological compounds for certain types of endometriosis and the high frequency of persistent or recurrent disease following both surgical and medical therapies. Due to the prevalence and relevance of the disease, there is urgent need to introduce new therapeutic agents in this field. Many progresses were done in the past 10 years on research in the pathogenesis of endometriosis, new treatments and possible adjuvant therapy. This review aimed to condense the most important and newer advances in the treatment for endometriosis. These new medical therapies would be used associated with surgical treatment and, in the future, will render possible the association of hormone therapy with non-hormonal treatment for endometriosis.

Current hormone treatments are able to suppress menstruation and induce endometrial atrophy, which is assumed to prevent further endometriotic tissue dissemination. They also reduce pain scores and some of them are well tolerated by most women. However, their anovulatory and contraceptive effects prevent their use by women seeking pregnancy, and they do not spare surgery in severe forms of endometriosis such as ovarian endometrioma and deep infiltrating disease. New hormonal drugs are expected to overcome these main limitations of standard hormonal drugs. The ideal treatment should relieve pain, induce regression of endometriotic lesions, even in the severe forms, and allow conception. In this perspective, the new therapeutic compounds based on progesterone receptor signaling such as SPRMs are unlikely to become first-line choices, as they share the same receptors and therapeutic mechanisms with existing drugs, including the potential contraceptive effect and the limited action on endometriotic lesions, which resist to progesterone due to the low expression of the stimulatory isoform of progesterone receptor [1,2]. As for GnRH antagonists, the perspective of innovation is limited because the therapeutic effect and the undesired side effects are very close to that of currently used GnRH agonists.

The new non-hormonal treatments reviewed here have in common the fact that none of them is targeted specifically to the endometrium or endometriosis. The positive side of this feature is that these drugs are already in routine use to treat or prevent other conditions and their potential benefits and safety profiles encourage their long-term use. However, the potential for side effects and the spectrum of contraindications is wide. Importantly, the use of novel anti-inflammatory agents, antioxidants, statins, insulin sensitizers, dopamine agonists and cannabinoid agonists has still to undergo clinical trials designed to test their effects in treating and/or preventing endometriosis. Meanwhile, they should not be used off-label with this specific purpose.

Further studies are necessary prior to include these novel agents in clinical practice, but it is clear that new perspectives exist to better treat patients with endometriosis, relieving their symptoms and improving their quality of life. In the years to come, in parallel with the assessment of these new drugs in clinical trials, another research branch should pursue the almost utopic aim of finding a molecular target that is specific to endometriotic lesions and once activated or blocked by drug therapy leads to implant involution, pain and inflammation cessation and fertility restoration.

Declaration of interest

The authors state no conflict of interest and have received no payment in preparation of this manuscript.
New trends for the medical treatment of endometriosis

Bibliography
Papers of special note have been highlighted as either of interest (•) or of considerable interest (★★) to readers.

This systematic review aimed to assess the efficacy and tolerability of the AI letrozole combined with norethisterone acetate vs norethisterone acetate alone in treating pain symptoms. The combination drug regimen was more effective in reducing pain and deep dyspareunia than norethisterone acetate. Letrozole caused a higher incidence of adverse effects, cost more and did not improve patients’ satisfaction or influence recurrence of pain.

AIs effectively reduce the severity of endometriosis-related pain symptoms.

This paper compared the efficacy and tolerability of the AI letrozole combined with norethisterone acetate vs norethisterone acetate alone in the treatment of pain symptoms caused by endometriosis. Hum Reprod 2009;24:3033-41

This systematic review aimed to assess the efficacy of AIs in treating pain symptoms caused by endometriosis. AIs effectively reduce the severity of endometriosis-related pain symptoms.

AIs effectively reduce the severity of endometriosis-related pain symptoms.
New trends for the medical treatment of endometriosis

- Pain may be due to nociceptive, inflammatory, or neuropathic mechanisms, and these mechanisms are relevant to endometriosis-associated pelvic pain. This paper provides a better understanding of the roles of these mechanisms in endometriosis.
- Antiprogestin and/or antiestrogen activity of PAs in primate models. Hum Reprod 1998;13:269-77
- The use of COX-2 selective inhibitors could be effective to suppress the establishment and growth of endometriosis, through their antiangiogenic activity.

This paper’s data provide evidence for a novel mechanism by which migration inhibitory factor can induce a pro-inflammatory phenotype in ectopic endometrial cells, and favor the establishment of endometriosis and its related clinical symptoms.

- Omega-9 fatty acids have an inhibitory effect on the secretion of inflammatory mediators such IL-8 and prostaglandins in HESC. EPA and DHA reduced IL-8 and prostaglandin E2 secretion and COX-2 mRNA expression in TNF-alpha-treated HESCs, supporting their effect as anti-inflammatory compounds.

Cyclic rhesus monkeys with low doses of the antiprogestin ZK 137 316: morphometric assessment of the uterus and oviduct. Hum Reprod 1998;13:269-77

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93. This paper evaluated the effects of simvastatin in endometrial stromal cells. Simvastatin induced apoptosis in human endometrial stromal cells. Simvastatin induced apoptosis and alters cytoskeleton and F-actin cytoskeleton.


99. Evidence suggests that medicinal herbs have direct actions on endometrial cells. This group found that a commonly used herbal formula exerted considerable antiproliferative effects. Extracts from this medicinal herbal mixture had direct effects on cell proliferation, apoptosis and CCL5 production in endometriotic stromal cells.


105. This group modified the resveratrol molecule and synthesized a number of compounds with different biochemical effects such as inhibition of tumor cell growth in various cell lines and inflammation pathways (COX activity).


New trends for the medical treatment of endometriosis


111. Jackson LW, Schisterman EF, et al. This paper clearly demonstrated that resveratrol induces apoptosis of tumoral cardiac HL1-NB cells, does not induce cell death on normal cardiomyocytes, and prevents norepinephrine-induced apoptosis on normal cardiomyocytes.


endometriosis. Fertil Steril 2011;95:1295-301

Targeting inflammation and angiogenesis with pioglitazone therapy limited the development of post-surgical adhesions associated with ectopic endometrial growth.


A prospective, randomized, placebo-controlled study was conducted in a baboon model to determine if a thiazolidinedione agonist of peroxisome proliferator-activated receptor-γ, pioglitazone, can impede the development of endometriosis.


129. Mckinnon BD, Bersinger NA, Mueller MD. Regulation of IL-6 in cultured endometrial stromal cells by thiazolidiones. Abstract Book. 11th World Congress on Endometriosis; 2011: p. 182


• Acupuncture treatment on specific acupuncture points appears to be an effective pain treatment for endometriosis, but this has to be confirmed in further study.

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• Acupuncture treatment on specific acupuncture points appears to be an effective pain treatment for endometriosis, but this has to be confirmed in further study.


• The paper’s findings suggest that the VEGF 936C/T polymorphism may be associated with the risk of endometriosis in a Caucasian population.


• The objective of this study was to analyze several microRNAs related to angiogenesis and the angiogenic factors, VEGF-A and thrombospondin-1 (TSP-1), in endometriotic lesions (ovarian endometrioma, peritoneal lesion and rectovaginal nodule) and eutopic endometrium from WEN.


144. Laschke MW, Menger MD. In vitro and in vivo approaches to study angiogenesis in the pathophysiology and therapy of endometriosis. Hum Reprod Update 2007;13:331-42


• Romidepsin targets VEGF at the transcriptional level, which subsequently leads to the reduction of secreted VEGF. This drug may be a potential therapeutic candidate against angiogenesis in endometriosis.


• ECGG from green tea has powerful antiangiogenic properties and inhibited the development of experimental endometriosis.


• Treatment with bevacizumab significantly inhibited endometriotic
lesion development, inhibited cell proliferation in lesions, reduced vascular density as well as increased the apoptotic cell percentage. Moreover, this drug reduced VEGF levels in peritoneal fluid of endometriosis-induced animals.


• The group data indicate an important role for bone marrow-derived endothelial cells in the pathogenesis of endometriosis and support the potential clinical use of antiangiogenic therapy as a novel treatment modality for this disease.


153. Novella-Maestre E, Carda C, Noguera I, et al. The treatment with carbegoline and quinagolide in an experimental mouse model of endometriosis demonstrated that neoangiogenesis was inhibited and the size of active endometriotic lesions, cellular proliferation index and angiogenic gene expression were significantly reduced by both dopamine agonists when compared with the placebo.


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