New perspectives for the treatment of endometriosis

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Abstract

Endometriosis is a chronic condition characterized by growth of endometrial tissue outside the uterus. Common symptoms include dysmenorrhea, dyspareunia, non-cyclic pelvic pain, and infertility. Endometriosis is often treated surgically upon diagnosis but with a higher rate of recurrence, suggesting that a combination of surgical and medical management might provide better outcomes. The primary goal of medical treatment is to interrupt the growth and activity of endometriosis lesions. Due to the chronic nature of this disease, long-term or repeated courses of medication may be required to control symptoms. Increasing knowledge about the pathogenesis of endometriosis at the cellular and molecular levels may give us the opportunity to use new, specific agents for treatment, including aromatase inhibitors, and new pharmaceutical agents affecting inflammation, oxidative stress, proliferation, angiogenesis and apoptosis. Many of these promising new agents may prevent or inhibit the development of endometriosis.

Key words: endometriosis, aromatase inhibitors, thiazolidinediones, omega-3, antiangiogenetic agents

Introduction

Endometriosis is a chronic condition characterized by growth of endometrial tissue in sites other than the uterine cavity, most commonly in the pelvic cavity, including the ovaries, the uterosacral ligaments, and pouch of Douglas. Common symptoms include dysmenorrhea, dyspareunia, non-cyclic pelvic pain, and infertility. The etiology is not known and is probably multifactorial, with a number of theories on how endometrial tissue occurs outside the uterus, including retrograde menstruation through the fallopian tubes, transport of tissue in the blood or lymph, and the local differentiation of mesothelial or blood cells into endometrium-like tissue [1]. For long time, the treatment of endometriosis has been based primarily on the radical removal of lesions. This is still a mainstay of therapy in cases of bowel and ureteral stenosis or adnexal masses with ultrasonographically doubtful characteristics. In the past two decades, a more pragmatic approach to the treatment of endometriosis has developed, centered more on the woman’s needs than on the extension of lesions. In other words, the problems of patients with endometriosis are disease-related symptoms and not implants per se, and treatments should be focused on resolution of complaints, independently of a priori excision of lesions. Current medical management of endometriosis is based on combined oral contraceptives, anti-inflammatory drugs, danazol, gonadotropin-releasing hormone (GnRH) analogues, progestins and steroids receptor modulators have been extensively used in clinical practice. Novel agents, that will hopefully improve the therapeutic potential, include aromatase inhibitors, immunomodulators, anti-inflammatory, antiangiogenic and antiproliferative agents [2].

Aromatase inhibitors

The aromatase enzyme catalyzes a terminal steroidogenesis step that leads to estrogen synthesis, by converting androgens into estrogens in a unidirectional pathway. Estrogen produced in extragonadal tissue acts locally at these sites as paracrine or even intracrine factors [3]. These sites include the mesenchymal cells of adipose tissue, breast, osteoblasts and chondrocytes of bone, the vascular endothelium and aortic smooth muscle cells, and numerous sites in the brain. The control of local estrogen production is modulated through the changes of aromatase. A non gonadal source of estrogen can sometimes contribute significantly to the circulating pool of estrogen, e.g. adipose tissue estrogen contribution. Sufficient circulating levels of the biologically active estrogen, estradiol, can be produced as a result of extraglandular aromatization of androstenedione to estrone that is subsequently reduced to estradiol in peripheral tissues. Such biologically active estradiol can activate several estrogen-dependent reproductive disorders including endometriosis, abnormal uterine bleeding, endometrial hyperplasia...
and cancer. Blocking estrogen production by inhibiting the enzyme catalyzing the main step of its synthesis from androgens (aromatase enzyme) is an exciting treatment modality for estrogen-dependent disorders. The third generation of aromatase inhibitors effectively block estrogen synthesis without exerting effects on other steroidogenic pathways and have been heralded as “a triumph in translational oncology”. They are highly selective and do not affect glucocorticoids, mineralcorticoids, or thyroxine secretion [4].

Significant levels of aromatase enzyme activity and expression have been detected in the stromal cell component of endometriosis. In addition, the eutopic endometrium of women with endometriosis has been found to contain low but significant levels of aromatase enzyme activity and expression [5].

The use of aromatase inhibitors for medical management of endometriosis is still experimental, two pilot studies examined pain relief after 6 months of daily treatment with an aromatase inhibitor together with high-dose norethindrone acetate or an oral contraceptive. Both showed significant (but not complete) resolution of pelvic pain in women with endometriosis who had not responded to first-line treatment. Since the women were premenopausal, the progestin or combined oral contraceptive was added to the aromatase inhibitor bone mass density was stable over the 6 months of the study. Further research is required to determine if aromatase inhibitors will be safe and effective for long-term use in women with endometriosis pain. Aromatase inhibitors are also believed to have the following roles in endometriosis-associated infertility: suppressing endometriotic lesions and ovarian stimulation agents [6]. In general, third generation aromatase inhibitors have been found very well tolerated with few significant side effects and a low rate of discontinuation due to adverse reactions. Most common side effects reported are: headaches, gastrointestinal symptoms, arthralgia and problems related to estrogen deprivation [7].

**Antiangiogenic agents**

Angiogenesis is an important component of the pathogenesis of endometriosis. Establishment of blood supply through angiogenesis seems to be a second basic step in the development of the disease after implantation of endometrial fragments in the peritoneal cavity [8]. The endometrium of women with endometriosis has an increased capacity to proliferate, implant and grow in the peritoneal cavity. Different antiangiogenic treatments such as anti-VEGF agents and other angiostatic drugs have been tested in experimental models of endometriosis with successful results inhibiting new vessels formation [9]. These drugs, mainly with cytotoxic properties, target specifically the endothelial cells without penetrate in the tissues. Angiostatic therapy can affect to various angiogenic response stages blocking: endothelial cell proliferation (TNP-470), endothelium-specific integrin survival signaling (vitaxin), extracellular matrix breakdown (batimastat) [10]. The vasculature is a promising target because of its genetic stability, easy access via the circulation and amplifying action during treatment [11]. Another major challenge of vascular therapy in endometriosis is developing more efficient drugs to target pericyte-coated vessels found in more advanced pelvic endometriotic lesions, as well as ovarian and rectovaginal endometriosis [12]. A part from the antiangiogenic substances, it has been shown that other products are effective in the VEGF system regulation. Interestingly, the severity of endometriosis has been directly correlated with spontaneous hyperprolactinemia or after stimulation with different agents. Prolactin (PRL) is a powerful angiogenic inductor and experimentally it induces angiogenesis in tissue like muscle [13]. The dopamine neurotransmitter, used in nontoxic levels, is able to promote the VEGFR-2 endocitosis in endothelial cells, blocking a critical step in the neoangiogenesis process. Similarly, dopamine agonists (as bromocriptin) extensively used in gynecology even during pregnancy, exert the same action. Moreover, if the relationship between neoangiogenesis and PRL is considered together with the relationship between PRL and endometriosis, and the expression of VEGF in ectopic endometrium, dopamine agonists are obvious candidates for the treatment of endometriosis [14].

**Anti-inflammatory and antioxidants agents**

There is substantial evidence that the pathogenesis of this condition involves increased concentrations of activated macrophages and changes in the cytokine network including interleukin-8 (IL-8), tumor necrosis factor α (TNF-α), monocyte chemoattractant protein-1 (MCP-1), transforming growth factors β (TGF-β) and several other proinflammatory chemoattractant cytokines (IL-1, IL-4, IL-5, IL-6, IL-10, IL-13, IL-15, INF γ...) [15]. Systemic inflammation may be induced by oxidative stress, another important component of endometriosis (Fig. 1) [16]. Leukocytes attracted to an activated by the above mentioned chemokines are a major source of oxidative stress. Furthermore, it appears that endometriosis is associated with depletion of antioxidant capacity. Intraperitoneal levels of vitamin E are decreased, likely due to consum-
ption by oxidant reactions. Another important consideration relates to the association of endometriosis with impaired immune recognition and clearance of ectopic endometrial cells, suppressed cytotoxicity of natural killer (NK) cells, as well as activation of B-cells accompanied by increased production of the antinuclear antibodies. Activation of the NF-κB pathway and disturbance of other anti-inflammatory mechanism lead to an overall inflammatory/angiogenic response with upregulation of several cytokines, MCP-1, VEGF, that are controlled by NF-κB [17].

A relationship between dietary fatty acids, dysmenorrhea and endometriosis has been recently suggested [18]. The most common are the n-3 fatty acids, a family of unsaturated fatty acids, including eicosapentaenoic acid (EPA; 20:5n-3) and docosahexaenoic acid (DHA; 22:6n-3), which share a common final carbon-carbon double bond in the n-3 position. Omega-3 polyunsaturated fatty acids have a role in the inflammatory process and a therapeutic effect has been suggested and the effect of two omega-3 fatty acids (DHA and EPA), on i) TNF-α induced IL-8 and PGE2 release and on ii) cyclooxygenase-2 (COX-2) mRNA expression, key enzyme for prostaglandin production were evaluated in human cultured endometrial stromal cells. The results show that DHA or EPA significantly reduced the lipopolysaccharide induced IL-8, and PGE2, release decreasing the expression of COX-2, underlying an inhibitory effect of omega-3 fatty acids on inflammatory mediators secretion, suggests a potential benefit in treatment of pelvic pain in patients with endometriosis (Fig. 2) [19].

The thiazolidinediones (TZDs), are a class of medications used in the treatment of diabetes mellitus type 2, introduced in the late 1990s. TZDs and have been shown to inhibit both monocyte migration and peritoneal inflammatory cells in a mouse model, decrease chemokine and cytokine expression in endometriotic stromal cells, and modulate angiogenesis.

Both rodent and baboon models of endometriosis have been utilized to demonstrate decreased endometriotic lesion burden with TZDs as compared with placebo. No human trial currently exists in the literature except preliminary recent data collected by limited series of patients (n = 6) with endometriosis treated with rosiglitazone for 6 months. While rosiglitazone has been given a black box

![Fig. 1. Oxidative stress and antioxidant](image1)

![Fig. 2. Inflammation and endometriosis: rationale for using omega-3](image2)

![Fig. 3. Inflammation and endometriosis: rationale for using thiazolidinediones](image3)
warning label from the FDA due to an increased risk of cardiovascular side effects in heart failure patients, pioglitazone remains on the market and might be a viable substitute. Since we are suggesting the possibility of using TZDs for endometriosis pain relief in conjunction with attempts to conceive, it must be understood that, under the current FDA safety classification scheme, TZDs are listed as a class C drug (Fig. 3) [20].

**Antiproliferative and proapoptosis agents**

Statins may be effective in the treatment of endometriosis, targeting growth and invasiveness of ectopic endometrial tissues as well as inflammation and oxidative stress associated with this condition [21]. Formation of endometriotic implants requires ectopic attachment and proliferation of endometrial stroma and glands. The rationale for considering statins as a promising treatment of endometriosis is based on several considerations: statins are competitive inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, a rate-limiting step of the mevalonate pathway, they decrease the mitogenic effect of IGF-I on endometrial stromal cells, moreover statins can interfere with angiogenesis (Fig. 4) [22].

In addition statins possess anti-inflammatory and immune-modulatory properties, which may reduce the inflammatory reaction associated with endometriosis. Another and related aspect of the action of the statins pertains to their anti-oxidant properties. Proliferation of endometrial stroma is stimulated by moderate oxidative stress, but inhibited by a broad range of antioxidant [23]. A recent study demonstrates that in cultures of human endometrial stroma: 1) simvastatin induces a wave of apoptosis and profound morphological changes including cell shrinkage and derangement of the cytoskeleton; and 2) these effects of simvastatin are abrogated in the presence of geranyl pyrophosphate (GGPP). The regulation of apoptotic death of endometrial stromal cells is likely to be an important mechanism controlling the growth of endometrial tissues [24].

**Conclusions**

Endometriosis remains a prevalent condition in women of reproductive age, characterized by the presence of endometrial tissue in extra-uterine sites, including the ovaries and other pelvic structures. In the absence of definitive cure, the management of endometriosis must be set within the framework of long-term therapeutic strategies. The medical treatment of endometriosis in the next future will be enriched by several possible strategies. Hormonal and anti-inflammatory drugs will be available in new formulations and their possible combination will be evaluated in order to defeat endometriosis.

**Author Disclosure Statement:**

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**References**


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