Endometriosis diagnosis and medical treatment: Present and future

Endometriosis diagnóstico y tratamiento médico: presente y futuro

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SUMMARY

The objective was to review the different diagnostic methods and medical treatments for endometriosis. It was reviewed the Latin-American and international bibliography using the Pub-Med, Google Scholar, Springer, the Cochrane Library, Embase, Scielo, Imbiomed-L, Redalyc, and Latindex web sites. The searches included the key-words: endometriosis, endometriotic, endometrial and ectopic endometrium, angiogenesis, angiogenesis and endometriosis, endometriosis and medical treatment, endometriosis and new treatment, GnRH agonist and antagonists, aromatase inhibitors, selective progesterone receptor modulators, anti-TNF α, antiangiogenic factors, and statins. Publications from 1970 to May 2020 were reviewed. Endometriosis is a disease that is still poorly understood. It is a complicated multifactorial syndrome and a common and painful pathology that affect women of reproductive age. Also, it is considered a debilitating disease that impacts the quality of life of an adult and adolescent patient. Diagnostic delays are common and may lead to a decline in reproductive potential and fertility. It was reviewed and analyzed the etiology, the risk factors, and the different mechanisms that have been mentioned and studied about its pathogenesis. Also, we reviewed the non-invasive, semi-invasive diagnostic methods that could be used in the future. Likewise, we analyzed the different types of treatment based on its pathogenesis.

Keywords: *Endometriosis, treatment, diagnostic methods, biomarkers, risk factors, epidemiology, pathogenesis.*

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RESUMEN

El objetivo fue revisar los diferentes métodos de diagnóstico y tratamientos para la endometriosis. Para ello fue revisada la bibliografía Latinoamericana e internacional usando los sitios electrónicos the PubMed, Google Scholar, Springer, the Cochrane Library, Embase, Scielo, Imbiomed-L, Redalyc and Latindex. La búsqueda se basó mediante el uso de las palabras claves: endometriosis, endometrio endometriótico, de cavidad endometrial y ectópico, angiogénesis, angiogénesis y endometriosis, endometriosis y tratamiento médico, endometriosis y nuevos tratamientos, agonistas y antagonistas de la GnRH, inhibidos de la aromatasa, moduladores selectivo del receptor de la progesterona, anti-TNF α, factores antiangiogénico y estatinas. Se revisaron los años comprendidos entre 1970 y mayo 2020. La endometriosis es una enfermedad poco entendida. Es un complicado síndrome multifactorial y una patología dolorosa común que afecta a la mujer en

edad reproductiva. También, es considerada como una enfermedad debilitante por el impacto que produce en la calidad de vida de las pacientes adultas y adolescentes. El retardo en el diagnóstico es frecuente y puede llevar a retardar el potencial de fertilidad y reproducción. Se revisó y analizó la etiología, los factores de riesgo y los diferentes mecanismos que han sido mencionados y estudiados sobre la patogenia. También, se revisó los métodos de diagnóstico no invasivos/semi-invasivos que podrían ser usados en el futuro. Asimismo, se analizó los diferentes tipos de tratamiento basados en su patogenía.

Palabras clave: *Endometriosis, tratamiento, métodos de diagnóstico, biomarcadores, factores de riesgo, epidemiología, patogenia.*

INTRODUCTION

The main purpose of endometriosis management is alleviating pain associated with the disease. This can be achieved surgically or medically, although in most women a combination of both is required. Long-term medical treatment is needed in most women; unfortunately, in most women, pain symptoms recur between 6 months and 12 months once treatment is stopped (1).

Current medical treatments are based on two mechanisms of action: anti-inflammatory and hormonal. Non-steroidal anti-inflammatory drugs (NSAIDs) are used commonly in women with dysmenorrhea, although there is not enough evidence to admit that they are effective in the treatment of endometriosis-related pain, and there is a lack of evidence to recommend one NSAID among the others (2,3). Hormonally active drugs act by blocking ovarian function and creating a more stable hormonal environment. Hormonal drugs currently used for the treatment of pain associated with endometriosis are hormonal contraceptives, progestogens and anti-progestogens, gonadotropin-releasing hor-mone (GnRH) agonists, and antagonists, and aromatase inhibitors.

Hormonal contraceptives reduce pain associated with endometriosis, by oral, transdermal, or vaginal administration. Progestogens: medroxyprogesterone acetate, oral or depot, dienogest, cyproterone acetate, norethisterone acetate, danazol, levonorgestrel intrauterine device, and anti-progestogens (gestrinone) are also recommended to reduce endometriosis-associated pain (4,5). GnRH agonists, with and without add-back therapy, are effective in the relief of endometriosis-associated pain but can be associated with severe side effects (4). There is insufficient evidence to recommend one among the others, as all hormonal drugs have shown efficacy in the treatment of pain associated with endometriosis. The clinical decision should take into consideration side effects, patient preferences, efficacy, costs, and availability (6).

All the drugs with proven efficacy in the treatment of pain associated with endometriosis are hormonal drugs and have contraceptive action. Endometriosis mainly affects women in their reproductive age; hence, these treatments can be inconvenient in the case of gestational desire. There is a need for new medications, effective in the treatment of pain, with an acceptable side effects profile, suitable for long-term use, with no contraceptive effect, and safe to use in the early pregnancy. Continuous efforts have been made to discover new drugs with higher efficacy, fewer side effects, and possible long-term treatment for those suffering from severe endometriosis.

MATERIAL AND METHODS

Literature searches were performed electronically in Pub-Med, Medline, ISI, DOAJ, Springer, Embase Web of Knowledge, DOAJ, Google Scholar, and the Cochrane Library for original articles written in the English language and Scielo, Lantidex, Imbiomed-L, Redalyc, and Google Scholar for original articles written in the Spanish language. Selection criteria included randomized clinical trials, observational trials, open-label non-randomized trials, and case reports related to medical treatments for endometriosis. The Cochrane Library was searched for reviews. Publications from 1970 to April 2020 were reviewed. Three hundred fifty references were found, and 140 references had the criteria of inclusion. The electronic search and eligibility of the studies were evaluated by the author.

The searches included the keywords:

endometriosis, endometriotic, endometrial and ectopic endometrium, angiogenesis, angiogenesis and endometriosis, endometriosis and medical treatment, endometriosis and new treatment, GnRH agonist and antagonists, aromatase inhibitors, selective progesterone receptor modulators, anti-TNF-α, anti-angiogenic factors, and statins.

Endometriosis

Endometriosis is a chronic, benign and estrogen-dependent pro-inflammatory gynecological disease, which is characterized by the presence of endometrial tissues, consisting of functional endometrial glands and stromal at anatomic sites outside the uterine cavity, especially the pelvic peritoneum and ovaries (7-9).

The prevalence of this disease is between 10 % to 15 % of women of reproductive age who suffer from the symptoms of endometriosis, but it can be as low as 1 % among asymptomatic women and as high as 60 %-80 % in women with Chronic Pelvic Pain (CPP), 20 %-50 % of women with infertility (10-12). It is estimated that more than 70 million women worldwide have endometriosis (13).

There are three different phenotypes of endometriosis, graded from the least to most severe, having different clinical and biological behaviors: 1. superficial peritoneal endometriosis (SUP); 2. ovarian endometrioma (OMA); and 3. deeply infiltrating endometriosis (DIE) — the latter is the most aggressive form, characterized by the involvement of the muscularis propia, irrespective of the anatomical location, DIE can penetrate >5 mm under the peritoneal surface (10,13,14). More than 90 % of the patient with DIE are associated with SUP (15,16) and all the OMA can have endometrial implants in the pelvic and intestine (17).

Endometriosis is a disease with multiple manifestations, very important repercussions, and a significant impact on the quality of life, reproductive future, and psychological well-being of the women with this pathology (10,12,15).

The most prominent symptoms of endometriosis are dyspareunia, dysmenorrhea, dyschezia, cyclic gastrointestinal/urinary symptoms, CPP,

and infertility. Up to 15 % of reproductive-aged women suffer from the symptoms of endometriosis (8,11,18-20).

A broad spectrum of pain symptoms ranging from no symptoms to severe symptoms (8,21). Endometriosis is also associated with an increased risk of certain cancer types and other chronic diseases, including ovarian, endometrial breast, lymphatic and skin cancer (22-24), cardiovascular diseases (25), autoimmune diseases (26), and allergic disorders.

Risk factors and epidemiology

Endometriosis has been clinically recognized since 1860 (27). As we mentioned before the prevalence Endometriosis varies widely: 0.7 %-15 % in population presenting for health care(10,11,20,28); 2 %-22 % in patients who undergoing to tubal ligation (28,29); 17 %-50 % of women with infertility (12,28,30), and 2 %-80 % in women with CPP (10,12, 28,31). The average annual incidence rate of newly diagnosed endometriosis was 7.2 (95 % CI 6.5–8.0) per 10 000 women aged 15–55 years (mean age at diagnosis:34). Incidence varied little throughout the 16 years, although there was a small but statistically significant annual percentage increase of 1.6 % per (95 % CI 1.1-2.2 %; P < 0.001), and these results of a large population-based study showed that 1.1 % of women were diagnosed with endometriosis (31).

Different factors have been consistently associated with the risk of developing endometriosis such as early age at menarche, short menstrual cycle length, prolonged menstrual flow, family history of endometriosis, infertility, intercourse during the menstrual period, caffeine intake, alcohol use, increasing age, taller height, and low body weight are associated with an increased risk (20,32,33-38). Rogers et al. (39) mentioned that women with lean BMI at age 18 (<18.5 kg/m) had a 20 % to 25 % greater risk of endometriosis compared to women with normal BMI (18.5-24.9 kg/m), 40 % greater than overweight women, and nearly double the risk of morbidly obese women (P<.0001). Recently, red hair, blue or green eyes, and freckles have been mentioned that increase the risk of endometriosis (16,20,40). While

parity, current oral contraceptive, tubal ligation, and smoking are associated with a decreased risk (20,32,41,42). Other lifestyle factors and dietary patterns that influence endometriosis risk may relate to their ability to mitigate inflammation. Physical activity and omega-3 dietary fatty acids may reduce levels of tumor necrosis factor-alpha (TNFα), interleukin 6 (IL6), and other inflammatory markers (43,44). While the association between physical activity and endometriosis is unclear (46), higher intake of long-chain omega-3 fatty acids have been associated with reduced endometriosis risk (47).

Etiology and pathogenesis

Etiology

The etiology and pathogenesis of endometriosis remain unclear. There are 3 classic mechanisms:

1. Retrograde menstruation theory

Approximately 75 %-90 % of women experience some retrograde intra-abdominal bleeding during menses (11,47). The development of endometriosis has been linked to exposure of the pelvic peritoneum to the blood products and cellular debris contained within menstrual fluids, which would normally be confined to the pelvis (47,48). Fur-thermore, menstrual fluid also contains some abnormal stem cells, which have been shown to have increased implantation and angiogenic capabilities and can form ectopic tissue lesions in animal models (48,49).

2. Coelomic metaplasia theory

Retrograde menstruation is the most widely accepted mechanism, but it cannot explain rare cases of endometriosis in the absence of a functioning uterus. The coelomic metaplasia theory proposes that endometriosis develops as a result of the transformation of mesothelial cells on the ovary to endometriotic gland cells (11,50). In fact, mesothelial inclusions are associated with endometriosis in the ovaries, fallopian tube, and pelvic wall. Rare cases of endometriosis described among men, pubertal and adolescent girls, and distant endometriosis in the thoracic cavity support this theory. Furthermore, an in vitro experimental model of human endometriosis demonstrated that ectopic lesions could result from metaplasia of the ovarian surface epithelium (11,51).

3. Lymphovascular metastasis theory

The theory of lymphatic and hematogenous spread has long been considered to explain the remote occurrence of the disease as well. According to this theory, exfoliated endometrial cells get into the venous drainage of the uterus, with subsequent deposition possible anywhere in the body. The theory is supported by the presence of endometriosis in the thoracic cavity and other distant sites outside the pelvis as well as detection of endometrial tissue in the uterine vessels in patients with adenomyosis. Lymphovascular metastasis remains a speculative explanation and, while possibly occurring during the development of endometriosis, is not likely to be the primary mechanism as cases of pulmonary and thoracic endometriosis are rare (11). Hormonally stimulated cyclical bleeding from the endometriotic tissue may contribute to the induction of a local inflammatory reaction and fibrous adhesion. It may result in an endometrioma or chocolate cyst in the case of deep implants in the ovary (52). Endometrial implants cause cellular and molecular variations. Ectopic implants respond to estrogen and progesterone, and a series of immunomodulators, inflammatory mediators, and proteins involved in oxidative progression enduring the last phases of the menstrual cycle are produced (53,54). An increase in the number of inflammatory cells and the production of inflammatory cytokines can cause pelvic inflammation owing to local and systemic responses of the immune system (55,56). Growth factors and inflammatory mediators secreted by peritoneal leukocytes are involved in the pathogenesis of the disease through an increase in the number of endometrial cells at ectopic sites, whereas many inflammatory cells and mediators, such as proteolytic enzymes, peritoneal macrophages, complement frag-ments, prostaglandins (PG), IL-1, and TNF, are produced in the peritoneal fluid of patients suffering from the disease (57).

Pathogenesis

It involves a complex interplay of genetic, anatomic, immunologic, and environmental factors (58,59); it is known that implantation, growth, and progression of endometriosis are caused by several disturbing biological mechanisms including invasion capacity, cell proliferation, apoptosis (60), immune function (14,61-63) as well as angiogenesis (64). Endometriotic implant nidation involves remodeling of the local peritoneal atmosphere facilitated by extracellular matrix-degrading proteases (65,66). Matrix metalloproteinases (MMPs) have a leading role in such tissue remodeling. Endometriotic lesions show the increased expression of MMP-1, MMP-3, and MMP-7 (14,67).

The increasing knowledge of several molecular pathways involved in the genesis of this chronic and progressive disease has pushed forward the investigation of new interesting targets. Studies focused on adhesion molecules, inflammatory and noninflammatory cytokines, angiogenic and growth factors, and glycoproteins, found to be highly related to the pathogenesis of endometriosis and the development of endometriotic lesions. Nevertheless, neither a single biomarker nor a panel of biomarkers has been confirmed as a consistent noninvasive test for endometriosis (68-70).

Inflammation

It has long been acknowledged by both researchers and clinicians that endometriosis is a disease associated with inflammation and elevated cytokine levels. Altered cytokine production by both cells of the immune system and the endometriotic lesion tissue has been proposed to contribute to these elevated cytokine levels (13).

Cellular mechanisms

Endometriosis has long been understood to be a disease of uncontrolled and aberrant growth of endometrial tissue. However, the cellular and molecular mechanisms that are disrupted in this disease remain to be defined.

The cell signaling pathways involved can be divided into those involved in proliferation and apoptosis, adhesion and invasion, angiogenesis, and immune function (11). Endometriosis is an inflammatory disease associated with abnormal T-cell function. IL-4, a cytokine produced by helper T-cells is significantly up-regulated in endometriotic lesions and can stimulate the proliferation of endometriotic cells (71). Th17 cells are also enriched in the peritoneal fluid of women with endometriosis as well as the ectopic endometrium. IL-17 has been shown to stimulate IL-8 and COX-2 expression thereby enhancing proliferation and migration of endometriotic cells (72).

Perhaps the most important component of immune dysregulation in endometriosis is mediated by the major histocompatibility complex (MHC). The MHC, also known as Human Leukocyte Antigens (HLA), are cell-surface proteins that mediate interactions between immune responsive cells. Aberrant expression of both Class I and II MHC antigens in endometriotic lesions inhibits the cytotoxic activity of natural killer cells (NK) (73,74). Some studies have suggested that the class I antigens HLA-B*07 and B*46 are associated with the development of endometriosis, whereas HLA-B*48 may offer a protective effect (75,76). Additionally, the class II HLA-DR antigens are aberrantly expressed in glandular cells of endometrium in endometriosis and adenomyosis and are thought to be involved in various immunological abnormalities (77,78). Non-classical HLA-G proteins have been suggested to be expressed on ectopic endometriotic cells and to play a critical role in the development of endometriosis through the suppression of NK function (79,80). However, other studies have reported that HLA-G is not expressed by endometrial cells at all (81). Despite what is known about altered MHC expression, it is equally plausible that abnormalities in NK receptors could lay the basis of an altered immune response in endometriosis (11).

Proliferation and apoptosis

The mechanisms regulating endometrial cell proliferation are primarily controlled by interactions between the sex steroids and their

receptors (82). Cyclical regulation of cellular proliferation by sex hormones is lost in endometriotic tissue. It is well-known, that alterations in cell cycle molecules such as cyclin and cyclin-dependent kinases are hormone-dependent (83) For example, FOXO1A, a transcription factor involved in cell cycle control and apoptosis, is regulated by progesterone, and its expression is significantly reduced in the endometrial tissue of women with endometriosis. Another cell cycle regulatory protein, ErbB-2 (TOB1) is also known to be down-regulated in women with endometriosis, which may be the result of increased interleukin (IL)-1β levels (11).

Growth factors also contribute to the increased proliferative potential of cells derived from endometriotic lesions. In fact, epidermal growth factor (EGF) is confirmed to stimulate proliferative activity in these cells (84,85). Mitogen inducible gene 6 (MIG6) is a negative regulator of EGF signaling. MIG6 is downregulated in women with endometriosis and may contribute to unmitigated growth of endometrial cells. Midkine (MK) is a member of the heparin-binding growth factor family that is over-expressed in the ectopic endometrium, which has been implicated in proliferation, migration, angiogenesis, and fibrinolysis (86).

The recurrent bleeding that is a hallmark feature of endometriosis leads to continual thrombin generation, which can subsequently stimulate the proliferation of endometriotic cells via protease-activated receptor 1 (PAR1). PAR1 downstream signaling induces expression of monocyte chemoattractant protein-1 (MCP1), TNFα, interleukins (IL), cyclooxygenase-2 (COX-2), MMP, hepatocyte growth factor (HGF), and tissue factor (TF) (82). Inhibition of COX-2 effectively reduces endometriotic epithelial cell proliferation (87). Furthermore, TNF-α, various interleukins, and HGF, which are known to be significantly elevated in the peritoneal fluid of women with endometriosis, also contribute to the proliferation of endometriotic cells (88). Leptin is primarily known as the protein released by fat cells. However, leptin is also found at elevated levels in the peritoneal fluid and serum of patients with endometriosis (89). Leptin expression can be stimulated by pro-inflammatory cytokines such as TNF-α and IL-1 and can, in turn, stimulate the proliferation of ectopic endometriotic cells (82,89). Besides the increased proliferation, the cells from endometriotic lesions are thought to have defects in apoptotic signaling pathways. The Aryl Hydrocarbon Receptor (AHR) also interacts with nuclear factor kappa-B (NF-ϰB) signaling pathways (90). The pleiotropic transcription factor, NF-ϰB has been identified to protect cells from apoptosis. The protein is constitutively active in endometriotic cells and its activation by lipopolysaccharide (LPS) can induce proliferation of endometriotic cells. B-cell lymphoma/leukemia-2 (Bcl-2) is a well-known anti-apoptotic signaling protein. In normal endometrium, Bcl-2 demonstrates cyclical expression decreasing during the menstrual and late proliferative phases, indicating hormonal regulation.

However, this regulation is lost in endometriosis (82). Conversely, expression of the pro-apoptotic protein Fas is unchanged while its ligand, FasL, is up regulated in endometriotic tissue as well as the peritoneal fluid of women with endometriosis (91). There is evidence to suggest that macrophage-derived growth factors, including platelet-derived growth factor and transforming growth factor-beta (TGF-β), may stimulate Fas-mediated apoptosis of immune cells, which may contribute to an immune-privileged environment for endometriotic cell survival (92). Also, the up-regulated expression of survivin decreased terminal effector caspases and DNA fragmentation factor 45 in endometriotic tissues may reflect resistance against apoptosis at ectopic sites (82). Watanabe et al. (93) demonstrated that survivin plays a critical role in the susceptibility of endometrial stromal cells (ESCs) to apoptosis. Survivin treatment of ESCs leads to a reduction of apoptosis inhibiting proteins, such as cIAP-1, XIAP, and survivin as well as an increase of apoptotic cells (93).

Adhesion and invasion

For endometriotic lesions to occur, the cells must invade and implant in distant locations. Increasingly, studies are noting roles for adhesions molecules and growth factors in this process. Cells derived from endometriotic lesions have increased adhesive capacity to various

components of the extracellular matrix (ECM) including collagen type IV, laminin, vitronectin, and fibronectin, whereas normal endometrium is more specific (11). In fact, in the early stages of endometriosis, attachment seems to be due to ECM degradation that could play a key role in the initiation of endometriosis (94).

The β-1 integrins and E-cadherin are both found in the endometrium (95). Aberrant expression of E-cadherin, β-catenin, and integrins has been reported in endometriosis. β-catenin plays a role in cell-to-cell adhesion and intracellular signaling binding to intracellular E-cadherin and connecting E-cadherin to the cytoskeleton of the cell (96). The E-cadherin–β-catenin complex plays a crucial role in epithelial cell–cell adhesion and in the maintenance of tissue architecture (97). Aberrant expression of cadherins and integrins is involved in the initiation and progression of human tumors (98). In the case of endometriosis, there are controversial reports about expression levels of these adhesion proteins. Poncelet et al. (99) have reported reduced expression of E-cadherin in ESCs. Loss of E-cadherin expression may be related to the local aggressiveness and invasiveness of peritoneal endometriotic lesions (97). Different authors have not found any altered expression of E-cadherins in peritoneal endometriotic lesions compared to eutopic endometrium, with no difference compared to proliferative endometrium (97,98). E-cadherin expression patterns in endometriotic tissues are contradictory and the role of E-cadherin in the development and progression of endometriosis is still unclear (11).

In recent studies, β-catenin has been shown that the reduced β-catenin expression could be involved in the pathogenesis of endometriosis contributing to its invasive character. Others have suggested that increased expression of β-catenin and activation of the Wnt/β-catenin complex may be a molecular mechanism of fibrosis in endometriosis (97,100,101). It has been shown the β-catenin expression is decreased. This implies that different alterations in the E-cadherin–β- catenin complex contribute to the pathogenesis of endometriosis (11).

Wnt/β-catenin complex regulates stem cell pluripotency and cell development, integrating signals from other pathways, such as TGF-β and FGF (Fibroblast growth factor), and targeting genes involved in cell migration and proliferation (101). In particular, TGF- β has been reported to be involved in the pathogenesis of endometriosis, playing a critical role in the migration and proliferation of fibroblasts to develop endometriotic lesions (102).

P-cadherin is the predominant cadherin subtype present in the human peritoneum and P-cadherin mRNA is significantly increased in peritoneal endometriotic lesions compared with eutopic endometrium, suggesting that P-cadherin may be involved in mediating endometrial–peritoneal cell interactions in the development of endometriosis (103).

Integrins mediate the adhesion of cells to ECM components, such as collagen types I and IV, fibronectin, and laminin. Integrins are a large family of transmembrane glycoproteins that have a dimeric structure of α and β sub-units and act as receptors for ECM components. Several studies are investigating the aberrant expression of integrins in endometriotic cells and their role in the invasion and attachment of ESCs to different components of the ECM (95). Higher levels of integrin of α1, α2, αv, β1, and β3 protein expression were observed in ESCs than in normal eutopic endometrial cells (NESCs). Data suggest that α6β1 could play a key role in the early phases of the development of endometriosis (104).

Osteopontin (OPN) is a glycoprotein involved in cell adhesion and migration by binding to integrins (105). OPN levels are increased in the blood and the ectopic endometrium of women with endometriosis (105). OPN is also speculated to influence migration and angiogenesis by regulating CD133+, also known as prominin-1, progenitor cells (105). The migration of these progenitor cells is thought to contribute to the establishment of distant endometriotic lesions.

Octamer-binding transcription factor 4 (OCT4) is a pluripotent factor that has been reported to be over-expressed in endometrial lesions (106,107). The expression of OCT4 may contribute to the pathology of ectopic endometrial growth by stimulating the migration activity of endometrial cells (106).

Matrix Metalloproteinases (MMPs) also contribute to cell migration via the breakdown

of ECM components and sub-sequent tissue remodeling. MMP-1, −2, −3, −7, and −9 are up-regulated in endometriosis and their expression is induced by cytokines such as IL-1, IL-8, and TNF- α (108,109). Furthermore, expression of tissue inhibitor of metalloproteinase-1 (TIMP-1) is decreased in the peritoneal fluid of women with endometriosis (110). TIMPs have been shown to control endometriotic cell migration induced by MMPs, suggesting that its down regulation is a major factor in the pathophysiology of endometriosis.

Angiogenesis

Angiogenesis of lesions is essential for endometriotic cell survival and development as observed for tumor growth, the two main regulators of angiogenesis are vascular endothelial growth factors (VEGF) and angiopoietins (111). VEGF is a key regulator of both physiological and pathological angiogenesis. VEGF is significantly increased in the peripheral blood, peritoneal fluid, and endometrium of patients with endometriosis, and its expression is known to be stimulated by a variety of cytokines, including IL-1(112). Inhibition of VEGF has been shown to lead to a significant decrease in the number of endometriotic lesions (113). Angiopoietin-1 (Ang-1) and Ang-2 are both increased in the endometrium of patients with endometriosis (111, 114). Ang-1 stimulates new vessel formation and Ang-2 can loosen cell-cell and cell-ECM contacts resulting in vessel remodeling.

Glycodelin is an endometrium-derived protein known for its angiogenic, immunosuppressive, and contraceptive effects. Glycodelin is thought to be involved in both the development of endometriosis and infertility associated with the disease (115). Glycodelin is produced in the glandular epithelium of secretory endometrium and is shed from endometriotic lesions into the peritoneal fluid and serum. These findings indicate that pro-angiogenic factors have important roles in the pathogenesis of endometriosis (116,117).

Oxidative Stress

Oxidative stress (OS) develops as a consequence of an imbalance between the generation of free radicals and the capacity of antioxidants. Free radicals are defined as any species with one or more unpaired electrons in the outer orbit (10,118). There are two types of free radicals: reactive oxygen species (ROS) and reactive nitrogen species (RNS). The main free radicals are the superoxide radical, hydrogen peroxide, hydroxyl, and singlet oxygen radicals. ROS are intermediate products of normal oxygen metabolism. Oxygen is required to support life; however, its metabolites can alter cell functions and/or endanger cell survival. OS results from an imbalance between ROS and antioxidants. ROS molecules are characterized by an unpaired electron and stabilize themselves by extracting electrons from different molecules in the body, such as lipids, nucleic acids, and proteins. Antioxidants are a defense mechanism created by the body to neutralize ROS. Serving as signaling molecules, ROS modify reproductive processes such as tubal function, oocyte maturation, and folliculogenesis (119).

Recent studies have investigated the role of the immune system and oxidative stress in the development of endometriosis (120). Some women with endometriosis seem to have an inefficient or altered cleansing mechanism, possibly attributable to a failure of the cellular and humoral immune response whose role is to inhibit the implantation of ectopic endometrial tissue (10).

Recent studies have identified a possible role for OS and ROS in this condition. ROS seems to alter endothelial cell permeability and adhesion molecule expression, triggering an inflammatory process. OS substances may contribute to the pathogenesis of endometriosis through the activation of macrophages. Activated macrophages can aggravate oxidative stress conditions through the production of lipid peroxides and other by-products of the reaction between apolipoproteins and peroxides. The sum of these events increases the concentrations of pro-inflammatory mediators, thus triggering inflammatory conditions in affected women (10,121-123). Recent studies have described a cause–effect relationship between epigenetic mechanisms and endometriosis development. In particular, aberrant DNA methylation and histone modification have been associated with an increased risk of endometriosis (10).

Diagnosis

Preliminary diagnosis of endometriosis is usually done based on clinical history since most women show normal results of physical examination. Clinicians palpate for uterine or adnexal tenderness, a retroverted fixture, nodulating uterosacral ligament, and any pelvic masses. Tenderness on palpation of the posterior fornix is the most common finding. Pelvic pain is also a symptom of other diseases such as pelvic adhesions, adenomyosis, and gastrointestinal or urologic disorders; therefore, differential diagnosis is important (7). Other causes of pelvic pain should be ruled out by carrying out appropriate diagnostic tests like urinalysis, Pap smear, pregnancy test, vaginal and endocervical swabs. Pelvic ultrasound scans are performed to facilitate the diagnosis of endometrioma, fibroids, and ovarian cysts (32). Pelvic masses are visualized using transvaginal and transabdominal ultrasound. Transvaginal ultrasound is used to better visualize endometrium and uterine cavity and detect ovarian endometriotic cysts but does not rule out peritoneal endometriosis, endometriosis-associated adhesions, and deep infiltrating endometriosis (32). Occasionally, magnetic resonance imaging and computed tomography scans are conducted to characterize the pelvic masses (124). Peterson et al. (20) mentioned that the 11 % (14/127) incidence of probable moderate/severe endometriosis diagnosed by MRI in the population cohort, but MRI was unable to reliably diagnose minimal/mild endometriosis.

Despite recent advances in identifying risk factors for endometriosis, the diagnosis of the disease cannot be based merely on physical examination and patient history. The diagnosis continues to be limited by a surgical diagnosis of the disease, often done by laparoscopic/laparotomy to visualize and confirm the presence of the endometrial implants in the female internal organs and the pelvic area. A positive histological confirmation is required to make the diagnosis, but negative histological results do not exclude it (32,125). Ultimately, the establishment of a defined set of endometriosis risk factors could lead to the identification of a group of women and girls with a high enough risk profile to warrant screening. Furthermore, these risk factors can also provide new insights into the etiology of the disease, which could lead to important advances in identifying potential screening biomarkers and treatment targets (32).

A noninvasive assessment for endometriosis is valuable for the early detection of endometriosis in symptomatic women who have pelvic pain and/or sub-fertility with normal ultrasound outcomes. Since laparoscopy is not practical as a first-line diagnostic tool, investigators have sought to identify non-invasive tools for early diagnosis that might prevent or delay the progression of endometriosis. Women with endometriosis show altered levels of CA-125, cytokines, angiogenic, and growth factors compared to normal women, but none of the markers have been proven to be a definitive clinical tool for diagnosis of endometriosis (32). Every day there is an improvement in the diagnostic methods of noninvasive or semi-invasive tests for endometriosis, with panels of identified peripheral blood biomarkers, protein markers revealed by miRNA, proteomics, and endometrial nerve fiber density.

Trials with high sensitivity and suitable specificity have been established; some have been confirmed in self-determining populations and are consequently promising (32,68). However, the range of blood tests that have been evaluated, a reliable test has yet to be identified for the diagnosis of endometriosis (126,127). A change in levels of analytes, proteins, microRNAs, and other markers corresponding to a disease state could be the basis for identifying novel biomarkers.

Biomarkers for the diagnosis of endometriosis

As aforementioned, the gold standard for confirmatory diagnosis of endometriosis is laparoscopic inspection with histologic confirmation after biopsy (128). However, laparoscopy may not be appropriate for all women with a history and physical examination suggestive of endometriosis. Therefore, care has been given to identifying simple and reliable biomarkers of endometriosis for early noninvasive or semi-invasive diagnosis of this disease. Many studies have evaluated the diagnostic value of biomarkers for endometriosis but to date, there are no reliable recommended biomarkers in endometrial tissue, menstrual or uterine fluids, and immunologic

markers in blood or urine for clinical use as a diagnostic test for endometriosis yet (32,129). Using semi or non-invasive diagnostic tools to evaluate biomarkers from blood, urine, or menstrual fluid, a surgical procedure could be avoided and women with endometriosis, except in patients who could benefit from surgery to increase fertility and decrease pain. Moreover, it provides data early in the disease process that could aid in treatment or prevent the progression of disease for women with a minimal-mild disease (69,70). A list of candidate biomarkers for endometriosis diagnosis and progression is summarized in Table 1. A combination of these biomarkers may improve the sensitivity and specificity of any single biomarker (129). Moreover, stem cell, proteomic and genomic studies could provide advanced opportunities for the discovery of potentially new reliable diagnostic biomarkers with high sensitivity for endometriosis.

Table 1

Potential diagnostic biomarkers for endometriosis

Biological groups	Biomarkers
Inflammatory markers-Cytokines	IL-1 β, IL-6, IL-8, IL-17, IL-21, RANTES, TNF-α, IFN-gamma, MCP-1, MIF, CRP
Steroids and hormones	ERs, 17 βHSD, aromatase
Growth factors	IGF, Activin, TGF β1, HGF, annexin-1
Cell adhesion and extracellular matrix molecules	Integrins, Vimentin, E-cadherin, osteopontin, ICAM-1 (CD54), β-catenin, FAK
Angiogenesis	VEGF, NGF, FGF-2, Leptin, IGFBP-3, glycodelin, M-CSF, angiopoeitin-1 and –2, MVD, endoglin and thrombospondin-1
Apoptosis and cell cycle control	Telomerase activity, Pak-1, cyclin D1, Survivin, Bcl-2, MCL-1, Bax, BclxL, Bcl-xS
Stem cell markers	CD9, CD34, Oct-4
Genomics	HOXA10, 3p, 5q, 7p, 9p, 11q, 16q, 17p, 17q, 18q, 19p, 19q
Proteomics	The analysis of different expression of certain peptides and proteins in endometriosis
Tissue remodeling	MMP-2, MMP9, TIMPs, urokinase

Regulated upon Activation, Normal T-cell Expressed and Secreted (RANTES), Monocyte chemotactic protein 1 (MCP-1), Vascular endothelial growth factor (VEGF), Microvessel density (MVD), Focal adhesion kinase (FAK), Insulin-like growth (IGF), Hepatocyte growth factor (HGF), Matrix metalloproteinase (MMP), Tissue inhibitors of metalloproteinases (TIMPs), Pak-1 (p21 activated kinase-1), 17 β hydroxysteroid dehydrogenase (17 βHSD), Estrogen receptors (ERs)

Treatment

Treatment of endometriosis-associated symptoms requires surgical and medical intervention (68). Although the available medical treatments are not completely therapeutic, they are a mainstay of pain suppression and reversion of lesions in women who suffer from this pathology.

Non-steroidal anti-inflammatory drugs/ Prostaglandin synthetase inhibitors

NSAIDs/Prostaglandin synthetase inhibitors (PGSIs) are used as the first-line treatment for pain. They are a heterogeneous group of non-steroidal inflammatory agents that inhibit the production of prostaglandins. PGSIs are

effective in the early stages of endometriosis, but lose efficacy when symptoms become more severe (130). Nevertheless, a lot of side effects such as skin reactions, bronchospasm, and serious blood dyscrasias have been reported for several of these drugs (131).

Hormonal therapy

Hormone therapy for endometriosis is frequently effective at reducing or even eliminating the pain of the disease. The primary mechanism of action of hormone therapy is to inhibit estrogen production (132). The success of various hormonal therapies depends on the localization and type of the endometriotic lesions. Superficial peritoneal and ovarian implants seem to respond better to hormone therapy than deep ovarian or peritoneal lesions or lesions within organs (132). Moreover, hormone treatment does not affect the adhesion of endometriotic cells and cannot improve fertility.

Oral contraceptives

Oral Contraceptives (OCPs) contain both estrogen and progesterone and regulate the monthly development of the endometrial lining. The use of OCPs has been suggested to reduce or eliminate the pain associated with endometriosis, making them an attractive long-term treatment option. The most common side effects of OCP treatment are acne, weight gain, and irregular withdrawal bleeding. The continuous use of oral contraceptives has been found to increase the risk of thromboembolism in some patients, for example, smokers aged more than 35 years or those who have a history of cardiovascular disease, and women trying to conceive (131).

Gonadotropin-releasing hormone (GnRH) agonists/antagonists

GnRH analogs are synthetic hormones that cause artificial menopause via inhibition of luteinizing hormone (LH) and follicle-stimulating hormone (FSH), which in turn decreases estrogen levels preventing menstruation. They can be administered as a nasal spray, by injection, or as an implant (132). GnRH agonist treatment can force endometriosis into long-term remission (133,134). The side-effects were reminiscent of menopause such as hot flashes, vaginal dryness, reduced libido, and osteoporosis (132). These long-term adverse effects can be minimized by co-administration (add-back regimes) of a low-dose estrogen or progestin hormone replacement therapy (HRT). GnRH-a generally is more effective to decrease estrogen levels more than danazol.

Progestogens

Progestogens are synthetic progesterone analogs that prevent ovulation. Both injectable progestogens such as medroxyprogesterone (Depo-Provera) and intrauterine systems such as a levonorgestrel intrauterine system (LNG-IUD/Mirena) have been successfully used to treat endometriosis (132). The most common side effects in patients using progestin treatment are bloating, acne, weight gain, spotting, irregular menstrual cycles, amenorrhea, and fluid retention. Progestin may affect the level of high-density lipoproteins in the blood, possibly enhancing the risk of cardiovascular side effects, such as thrombosis (135). The LNG-IUD is a long-acting contraceptive method, which acts through a steady low level of LNG in the peripheral circulation. This IUD is used as a treatment for dysmenorrhea, menorrhagia, and endometriosis (136).

LNG-IUD appears to have a direct effect on the growth of endometriotic implants (136). The suppression of menstruation, or marked reduction of flow, may also be beneficial in reducing the amount of ret-rograde menstruation. One of the side effects of the LNG- IUD is thinning of the endometrium, which causes a decrease in menstrual blood loss and a high incidence of amenorrhea.

Antiprogestogens

Also known as synthetic testosterone derivatives, anti-progestogens are synthetic hormones that bring on artificial menopause by decreasing the production of estrogen and progesterone. Anti-progestogens suppress the growth of the endometrium and the

symptoms of endometriosis by blocking the production of ovarian-stimulating hormones (LH and FSH) (132). Among the side effects of antipro-gestogens, we can find acne, weight gain, hot flushes, fatigue, mood changes, and the development of masculine features such as hirsutism and a deepening voice. Also, its possible role in increasing low-density lipoprotein cholesterol levels and its conceivable involvement in ovarian cancer (137,138).

Aromatase inhibitors

Aromatase is a key enzyme in synthesizing estrogens from androgens, being involved in the conversion of androstenedione and testosterone to estrone and estradiol, respectively. Several studies suggest that aromatase is inappro-priately expressed in the eutopic endometrium and ectopic endometrial implants in women with endometriosis but the expression in endometriotic tissue is still subject to some debate since the presence of aromatase by these tissues has not been confirmed by other studies (139).

The studies published do not show clear evidence of the effectiveness of aromatase inhibitors for the treatment of pain related to endometriosis. The European Society of Human Reproduction and Embryology (ESHRE) in their latest guidelines recommend the use of aromatase inhibitors such as anastrozole or letrozole, associated with another hormonal treatment (oral contraceptive pills, progestogens, or GnRH analogs) only in women in whom all surgical and medical treatments have failed (5). The side effects most commonly associated with the treatment with aromatase inhibitors are artificial menopause such as hot flashes, mood changes, muscle aches, vaginal dryness, and breakthrough bleeding. Estradiol levels are significantly suppressed with the treatment. Major limitations to their use are recurrences after finishing treatment, severe side effects, and cost (140).

Selective progesterone receptor modulators

Selective progesterone receptor modulators (SPRMs) are defined as a new class of progesterone receptor ligands, which exhibit both progesterone agonistic and antagonistic activities (18,141). In the absence of progesterone, the SPRMs act like weak progestins. In the presence of progesterone, they may also show weak anti-progestogenic properties in some tissues, particularly in the endometrium. This property justifies their use in the treatment of myomas and endometriosis. Only two drugs are currently approved for gynecologic use. Mifepristone is approved for the termination of pregnancy, cervical dilation, medical termination of pregnancy during the second trimester, and fetal death in the uterus (142). Mifepristone at 50 mg daily dose has been shown to improve pain and cause regression of endometriosis implants (143) but at a lower dose is unable to control the growth of endometriosis lesions (144). Ulipristal acetate has been approved in Europe and the United States as an emergency contraceptive, and recently the European Commission has also approved ulipristal acetate for the preoperative treatment of uterine fibroids (145). Ulipristal has been used to treat the pain produced by endometriosis implants and the doses recommended are between 5-15 mg (146). Other SPRMs that it has been used in a randomized placebo-controlled clinical trial are asoprisnil to treat patients with moderate or severe pain for 12 weeks. Using doses between 5 to 25 mg reduced the pain (147). There were no laboratories or clinical signs of low estrogen.

Common side effects of SPRMs are headache, abdominal pain, and tenderness. They induce endometrial changes known as progesterone receptor modulator-associated endometrial changes (PAECs). The levels of estrogens are maintained, and BMD is not affected.

The potential benefit of SPRMs in the management of pain associated with endometriosis, and the long-term security and endometrial changes associated must be clarified. SPRMs seems to be a promising medical treatment in endometriosis (18).

Anti-tumor necrosis factor-α

Endometriotic tissue is an inflammatory process, which is mediated by the overproduction of prostaglandins, metalloproteinases, cytokines, and chemokines. Increased levels of acute inflammatory cytokines such as IL-1β, IL-6,

and TNF-α are detected in the peritoneal fluid of women with endometriosis, and probably enhance the adhesion of shed endometrial-tissue fragments onto peritoneal surfaces (148). A non-hormonal alternative in endometriosis treatment could be modulating inflammation through TNF-α blockers such as recombinant human TNF-α binding protein (149) which is currently used in other inflammatory diseases such as Crohn's disease or rheumatoid arthritis. One of these medications is infliximab. There is not enough evidence to recommend the use of anti-TNF-α drugs for the treatment of pain associated with endometriosis. More number of blind randomized controlled trials should be developed to define the role of infliximab in the treatment of pain associated with endometriosis, either before or after surgery, and compare it with other medical treatments and other anti-TNF-α drug (18,150).

Thiazolidinediones

Two thiazolidinediones (TZDs), rosiglitazone and pioglitazone, were developed for the treatment of diabetes mellitus due to their ability to increase insulin sensitivity. These medications are TZDs are a class of drugs that may show promise in treating endometriosis-induced pain while, contemporaneously, allowing these women the chance to conceive (151). Their mechanism is not fully understood, but studies show they bind to and activate peroxisome proliferator-activated receptor-gamma, found in many tissues throughout the body, including endometrial epithelial and stromal cells (152,153). TZDs have been shown to inhibit both monocyte migration and peritoneal inflammatory cells in a mouse model (81,154-156), decrease chemokine and cytokine expression in endometriotic stromal cells (152,153) and modulate angiogenesis (157). Moravek et al. (151) reported the improvement in 3 patients with pain after 6 months of treatment with TZDs. They mentioned that future studies should assess more objective measures of the extent of endometriosis using laparoscopy.

Matrix metalloproteinase inhibitors

Identification and targeting of more specific mediators in the development and/or progression of endometriosis may lead to the development of more desirable and effective treatment regimes. One potential target area is the MMP system as these proteases have been postulated to play a role in the establishment and progression of the disease. The use of anti-TNF-α agents to treat endometriosis-associated infertility and suppress endometriotic implant growth has been suggested (50-52). One potential mecha-nism by which anti-TNF-a therapies may elicit their effect is through the inhibition of MMP transcription. TNF-α is a potent stimulator of MMP expression in endometrial and endometriotic tissue (158). It is postulated that cytokines such as TNF-α, which are elevated in the peritoneal fluid of women with endometriosis, stimulate MMP expression by retrogradely shed endometrial tissue and allow for the development and progression of ectopic endometrial tissue growth/endometriosis; by blocking the production or action of this cytokine, subsequent induction and actions of MMPs would be inhibited. Potential anti-TNF-α therapies may include pentoxifylline, leflunomide, etanercept, Infliximab, and recombinant human TNF binding protein-1. The potential use of anti-TNF-α therapies in endometriosis continues to be studied in animal models may someday be herald as the next wave of endometriosis treatment (158).

Recombinant interferon (IFN)-alpha-2b

It has been suggested that IFN-α-2b may activate macrophages that help in the suppression of endometriosis growth (159). Several experimental studies in rats using IFN-alfa-2b have found that rat recombinant human IFN-alfa-2b reduces experimentally induced endometriosis in rats (159,160). The findings show that recombinant IFN-alfa-2b has regressed significantly both the size and histological components of the endometriotic implants in rats.

Ali et al. (161) administered a laparoscopic intraperitoneal injection of IFN-α-2b to women with pelvic endometriosis. Twenty-five infertile women with stages II, III, or IV disease were enrolled. Second-look laparoscopy was done 3 months later to evaluate the effects of the treatment. They found out that at the 3-month follow-up examination, all symptoms and signs, including CA-125 levels, had decreased

significantly. The decrease was proportional to the size and diameter of large implants and the degree of endometriosis. However, more studies are needed for better evaluation of this medication in the treatment of endometriosis.

Antiangiogenic factors

Besides, endometriosis is considered an inflammatory disease, it is also classified as an angiogenic disease. The retrograde menstruation theory explains the pathogenesis of endometriosis due to retrograde menstruation of endometrial tissue, rich in angiogenic growth factors, which implants in the peritoneum (11,162) The endometrium from patients with endometriosis reveals a higher angiogenic activity than the endometrium from healthy women, the same as is found in endometriotic lesions and peritoneal fluid from women with endometriosis (163-165). Several studies concentrate on antiangiogenic compounds as a promising therapy for endometriosis (166). The future in antiangiogenic therapy for endometriosis seems to be factors that blockade different pathways in the angiogenic cascade (18).

Growth factor inhibitors

One of the most studied angiogenic factors is the vascular endothelial growth factor (VEGF). The development of anti-VEGF antibodies has proved in vitro efficacy in preventing the establishment of endometriotic lesions (113,167,168). Bevacizumab has demonstrated in vitro activity against endometriotic lesions (169), but clinical application appears to be limited because of its severe side effects, which include hypertension, proteinuria, hemorrhage and thrombosis, and gastrointestinal perforation (170). Another antiangiogenic factor, 2-methoxyestradiol, tested in studies for cancer, suppresses lesion growth with minimal toxicity (171). Pharmacokinetic problems due to their extensive first-pass metabolism should be resolved before new clinical trials are conducted.

Endogenous angiogenesis inhibitors

Endostatin is an endogenous antiangiogenic factor that inhibits the development of new vessels. Some studies have shown the inhibition of developing endometriotic lesions (168) without affecting fertility (172). Angiostatin, another endogenous inhibitor of angiogenesis, has been used to treat endometriotic lesions in mice. Its proteolytic mechanism plays a critical role in the downregulation of angiogenesis. But the antiangiogenic mechanism of angiostatin remains an enigma (173). Without knowing the mechanisms, it is difficult to predict the outcome of ongoing clinical trials.

Fumagillin analog

Fumagillin, an antibiotic produced by Aspergillus fumigatus, shows antiangiogenic activity. Some synthetic derivatives have been developed as well. The only calpastatin that shows the same antiangiogenic activity in endometriosis lesions without toxic effects included the neurotoxicity in the female reproductive system. It could be a candidate for future research in antiangiogenic therapy for endometriosis (18).

Immunomodulators: pentoxifylline

Changes in the immune system play an essential role in the pathogenesis of endometriosis (174). For that reason, immune-modulatory agents, such as pentoxifylline, have been suggested for the treatment of endometriosis. Pentoxifylline has shown anti-angiogenic effects in the development of endometriotic lesions in rats (175), is well-tolerated, and does not inhibit ovulation (176). Although there is some clinical trial published comparing the use of pentoxifylline with placebo after conservative surgery (177), there was not found any evidence of an increase in clinical pregnancy or improvement in pain scores. Adverse events were not reported. A recent Cochrane review concluded that there is little evidence to support using pentoxifylline as a treatment for subfertility in women with endometriosis at this time (177).

Statins

Statins are potent inhibitors of cholesterol biosynthesis to reduce serum cholesterol in patients with hyperlipidemia and are competitive and reversible inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase, the key enzyme in the mevalonate pathway to block the conversion of HMG-CoA to L-mevalonate, a rate-limiting step in cholesterol synthesis. They can downregulate products of the mevalonate pathway, such as farnesyl diphosphate and geranyl diphosphate, which may contribute to regulating tumor cell growth, motility, and differentiation (178,179).

The mechanisms of action of statins on the development and growth of endometriosis in animal models are yet to be elucidated; however, several possible effects may be involved including inhibition of endometrial stromal growth, decreased angiogenesis, reduced adherence, and invasion of the peritoneum, as well as decreased oxidative stress and inflammation.

Also, statins, lipid-lowering drugs, have shown anti-angiogenic activity in high doses. Statins exhibit anti-inflammatory, antioxidant, and immunomodulatory properties, decreasing mediators and markers of inflammation (i.e., C-reactive protein, TNF-α, interleukins, and MCP-1) (180). Statins also inhibit the MMPs and increase tissue inhibitors of metalloproteinases, an enzyme system that regulates normal extracellular matrix remodeling, which is dysregulated in endometriosis (181,182). Several authors (180,183-185) have shown that statins inhibit the growth and invasiveness of human endometrial stromal (HES) cells in vitro. Most of the studies about statins (Atorvastatin, Simvastatin, Lovastatin, Rosuvastatin) have been done in vitro and animals such as rodents, rabbits, baboons, and have shown that statins are effective in reducing endometriotic lesions (186,187). Studies in vitro have demonstrated that simvastatin induced a concentration-dependent inhibition of HES cell proliferation, evidenced by reduced DNA synthesis and a decrease in the number of viable cells (188). Simvastatin induced a dose-dependent decrease in the number and size of endometrial implants in mice in a mouse model. At the highest dose of simvastatin, the number

of endometrial implants decreased by 87 % and the volume by 98 % (178). The study has also shown that simvastatin inhibits the proliferation of stromal cells derived from human endometriotic implants in ovaries (189). Studies in vitro with atorvastatin have demonstrated antiangiogenic activity in endometriotic lesions, without side effects on reproductive function. More studies are necessary to ascertain which statin is the most suitable for the antiangiogenic treatment of endometriosis and to achieve antiangiogenic activity at nontoxic doses (18,180). Yilmaz et al. (190) showed that atorvastatin reduced the size of endometrial implants in rats, which was supported in this study by the histological, immunohistochemical, and biochemical findings Also, intraperitoneal atorvastatin seems to be more effective than the oral one. Further experimental and clinical studies should be undertaken to assess the effect of atorvastatin on endometriosis with different doses and routes of administration.

However, the mechanisms of action of statins on the development and growth of endometriosis in animal models are yet to be elucidated; however, several possible effects may be involved including inhibition of endometrial stromal growth, decreased angiogenesis, reduced adherence, and invasion of the peritoneum, as well as decreased oxidative stress and inflammation.

Little is known about the effects of statins on endometriosis in women with this disease. There is only one study that evaluated the effects of statin on women with endometriosis. In that study, postoperative pain was evaluated in 60 patients who have undergone laparoscopic surgery for endometriosis followed by a 16-week course of simvastatin or GnRH analog. In both groups, there was a significant and comparable reduction of pain at 6 months after surgery (179).

Almassinokiani et al. (179) found after conservative surgical treatment that given simvastatin 20 mg daily for 4 months was similar to decapeptyl 3.75 mg IM for 4 doses to the control group.

These findings suggested that the use of statins for the treatment of endometriosis can be effective.

In summary, the findings indicate that the use of statin in the treatment of endometriosis

holds promise. This possibility is particularly exciting given the excellent safety record and minimal side effects of statins. Future studies may require either work on the primate model, such as baboon, or clinical trials in women with endometriosis. A further large-scale human randomized clinical trial with more appropriate endpoints is necessary to confirm whether statins may truly be enchanted pills for the conservative treatment of endometriosis (191).

CONCLUSION

Endometriosis is a disease that is still poorly understood (187), a complicated multifactorial syndrome, and a common and painful pathology that affect women of reproductive age. Also, it is considered a debilitating disease that impacts the quality of life of an adult and adolescent patient (11,32). Diagnostic delays are common and may lead to a decline in reproductive potential and fertility (32).

Through elucidation of the molecular and cellular regulation of endometrial growth and endometriosis, and the genetic and immunologic factors allow us to know and to understand its pathophysiology. Because of that, the advancement of genomic and proteomic data will facilitate the development of non-invasive diagnostic biomarkers as well as therapeutics that target the pathophysiology of the disease and halt, or even reverse, the progression (187). A semi/non-invasive diagnostic biomarker would be a useful tool to identify patients early in the disease process and thus improving outcomes, including less pain and better fertility. A myriad of biomarkers has been associated with endometriosis; however, they are not sensitive and specific enough for use in screening. These potential biomarkers would reduce the cost of surgical intervention by early diagnosing the cases and thus improve clinical management of the disease. Therefore, more research is needed in this area of medicine.

Declaration of Conflicts of Interest

The author declares that there are no conflicts of interest in the preparation of this review.

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