Angiogenesis signaling in endometriosis: Molecules, diagnosis and treatment (Review)

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Abstract. Endometriosis (EM) is one of the most common diseases among women of reproductive age. The etiology and pathogenesis of EM remain unclear and therefore there is a lack of effective treatment measures, which affects physical and mental health, as well as the quality of life of patients with EM. Angiogenesis has become a hotspot for research on the pathogenesis of EM; the role of angiogenesis-related serological markers and anti-angiogenic therapy in the diagnosis and treatment of EM is promising for early diagnosis and treatment of EM. Angiogenesis in EM is subject to complex regulation by hormones, immunity and associated cytokines. Therefore, novel targets for angiogenesis therapy are also being discovered and developed. The present review summarized the pathological mechanisms of angiogenesis and the value of relevant markers in pathogenesis and diagnosis of EM, along with the status of research on anti-angiogenic drugs in the treatment of EM. The role of angiogenesis in EM provides an important reference for treatment and diagnosis, but there is no uniform non-invasive diagnostic marker and proven strategy for anti-angiogenesis.

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Abbreviations: AT1R, angiotensin II type 1 receptor; COX-2, cyclooxygenase 2; DC, dendritic cell; D2-ag, dopamine receptor agonist; E-MSC, endometrial mesenchymal stromal cell; EM, endometriosis; ESC, endometrial stromal cell; ERβ, estrogen receptor β; FGA, fibrinogen α chain; FGF, fibroblast growth factor; Th17, helper T 17; HIF-1α, hypoxia-inducible factor-1α; ICAM-1, intercellular adhesion molecule-1; LPS, lipopolysaccharide; MMP, matrix metalloproteinase; NF-κB, nuclear factor-κB; PPARγ, peroxisome proliferator-activated receptor γ; PDGF, platelet-derived growth factor; PGE2, prostaglandin E2; RAPA, rapamycin; ROS, reactive oxygen species; TNF-α, tumor necrosis factor-α; TFG-β, transforming growth factor-β; sVCAM-1, soluble vascular cell adhesion molecule-1; VEGF, vascular endothelial growth factor

Key words: endometriosis, angiogenesis, diagnosis, biomarkers, anti-angiogenic

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1. Introduction

Endometriosis (EM) is an estrogen-dependent disorder characterized by the presence of endometrioid epithelium and glands outside the endometrium and myometrium (1). It affects 10-15% of women of reproductive age worldwide and is one of the most frequently occurring diseases among this group (1). The main clinical manifestation of EM is pain, including typical but non-specific pain, such as dysmenorrhea and chronic pelvic pain, and ~1/3 of patients have infertility, with advanced EM potentially leading to gynecological malignancy, such as ovarian cancer (2,3). The lack of specific clinical manifestations of EM makes it difficult to differentiate from conditions characterized by chronic pelvic pain in clinical practice, which makes the diagnosis and treatment of EM challenging (3). This results in psychological burden to patients and affects physical and mental health, as well as their quality of life (4,5).

The pathophysiology of EM disease is not thoroughly understood. The potential pathogenesis of EM is hypothesized to involve retrograde menstruation, uterine stem cells and somatic epithelium (1). Among them, the theory of retrograde menstruation is the leading theory of the pathogenesis of EM (6). However, development of EM is associated with immune alterations and a proinflammatory peritoneal milieu, which determines the progression to EM (7). It is noteworthy that the formation and growth of ectopic lesions depends on nutrient support, with neovascularization serving an important role in the development of endothelial ectopic lesions (2,8). Vascular permeability is notably increased in ectopic lesions

of EM and a large number of new blood vessels appear (2). This indicates that angiogenesis is a key link in the pathogenesis of EM, which represents a potential target for development of future diagnostic and therapeutic strategies. Recent study of angiogenic mechanisms in EM has revealed the importance and potential role of angiogenesis-related pathways and markers of EM for diagnosis and treatment (9-12). That has provided a new direction for the discovery of novel targets of anti-angiogenic action and therapy and novel lines of thought and strategies for clinical treatment of EM.

The present review aimed to summarize advances in the investigation of EM angiogenesis, including availability of non-invasive molecular markers for the diagnosis of EM, for the potential clinical value of anti-angiogenic therapy as an alternative to non-hormonal therapies for treatment of EM.

2. Search methods

Literature searches were performed in PubMed (pubmed.ncbi.nlm.nih.gov/) and ISI Web of Knowledge (webofscience.com) for English articles with the key words 'endometriosis', 'endometriotic lesions', 'angiogenesis', 'vascularization', 'anti-angiogenic', 'anti-angiogenesis', 'anti-angiogenic therapy' and 'diagnosis'. The search included animal and human studies focusing on EM angiogenesis, diagnosis and treatment, and no restriction was set regarding the publication date.

3. Angiogenesis in EM

Angiogenesis is defined as generating new blood vessels from the germination of pre-existing vessels. This is initiated by vascular endothelial growth factor (VEGF), which activates resting endothelial cells in microvasculature to release matrix metalloproteinase (MMP), thereby mediating degradation of the vascular basal membrane so that endothelial cells migrate into the surrounding tissue; additionally, tubular branches of endothelial cells form vascular rings and novel basement membranes, ultimately leading to new vessel formation (13). Angiogenesis is key for normal physiological processes by spontaneous endometrial thickening and development, serving an important role in the menstrual cycle (14). In patients with EM, the endometrium forces menstrual blood to the peritoneal cavity leading to induction of oxidative stress and immune responses, releasing related inflammatory factors and cytokines. This results in disrupted homeostasis of the peritoneal microenvironment and a relative increase in pro-angiogenic factors, which leads to neovascularization of ectopic endometrial vessels and establishment of the microvascular network (2,15). EM lesions develop in a complex and dynamic environment that is regulated by a number of molecules, cytokines and associated signaling pathways (Table I) (16).

Role of inflammatory cells in angiogenesis progression in EM. At present, although the etiology of EM is unclear, immune dysfunction has been cited as a key contributing factor in the growth of ectopic lesions of endometrial debris following retrograde menstruation (17,18). Density of immunocompetent cells such as T lymphocytes, natural killer cells, dendritic cells (DCs), macrophages and neutrophils is markedly increased in EM lesions and the peritoneal cavity (Fig. 1) (17,19). Abnormal alterations in inflammatory and immune cells cause alterations in cytokines in the peritoneal fluid of patients with EM. Compared with healthy patients, the expression of interleukin (IL) -1β, -6, -8, -10 and -17, tumor necrosis factor-α (TNF-α) and macrophage migration inhibitory factor is notably elevated in the peritoneal cavity or serum of patients with EM (20-27). These cytokines are not only involved in the chronic inflammatory response to EM, but also promote the implantation and growth of ectopic lesions by upregulating expression of cyclooxygenase 2 (COX-2) and/or VEGF.

Previous studies have suggested that enhanced concentration of neutrophils in the peritoneal fluid of patients with EM may be the result of elevated concentrations of potent neutrophil chemokines, such as IL-8, in plasma and peritoneal fluid (28,29). Moreover, neutrophils secrete cytokines such as VEGF and IL-8 and -17 to promote the proliferation and invasion of endometriotic cells and angiogenesis (30). In this process, estrogen is involved in neutrophil activation, and it was found that *in vitro* culture in the presence of IL-6, TNF-α, lipopolysaccharide (LPS) and estrogen-enhanced VEGF release from isolated peritoneal macrophages and neutrophils (31). Conversely, inhibition of estrogen signaling activity decreases the number of neutrophils and expression of proinflammatory cytokines, thereby inhibiting the progression of EM (32).

Immune dysfunction characterized by hyperactive peritoneal macrophages with altered phagocytic ability represents a key point in EM angiogenesis (33,34). Macrophages are hypothesized to be one of the sources of VEGF and fibroblast growth factor (FGF), which promote the growth of diseased blood vessels in EM and accelerate the process of EM development (24). Previous studies have found that accumulated macrophages are recruited to the ectopic environment, primarily using the alternatively activated macrophage (M2) phenotype, which promotes and enhances proliferation and clonogenic capacity of endometrial stromal cells (ESCs) (33-36). Additionally, M2 cells produce a variety of stimulating factors to induce peritoneal inflammation, thus forming a complex loop of regulatory mechanisms to maintain the altered peritoneal microenvironment of EM to promote immune escape, adhesion and angiogenesis of the ectopic endothelium (31,37). By contrast, nanovesicles derived from M1 macrophages directly or indirectly inhibit migration and invasion of endometrial mesenchymal stromal cells (E-MSCs) to decrease formation of blood vessels (35).

Contrary to macrophages, the role of DCs in pathogenesis of EM is not yet clear. Suen *et al* (38) showed that IL-10 secreted by plasma cell-like DCs enhances ESC migration and promotes angiogenesis via the secretion of pro-angiogenic factors, leading to the growth of endometriotic lesions. Furthermore, DCs may promote EM angiogenesis by secreting cytokines such as IL-6 and -12 and transforming growth factor-β (TGF-β) (39).

Regulatory T cells and helper T 17 (Th17) cells are essential for immune defense and immune homeostasis (18). Imbalance in expression of Th2 and Th1 cells is one of the essential promoters of ectopic endothelial growth (40). Th17 cells produce IL-17, a strong proinflammatory mediator that stimulates expression of angiogenic and proinflammatory cytokines, and promotes angiogenesis in the ectopic endothelium (30,41). *In vitro* results suggest that IL-17 may be a

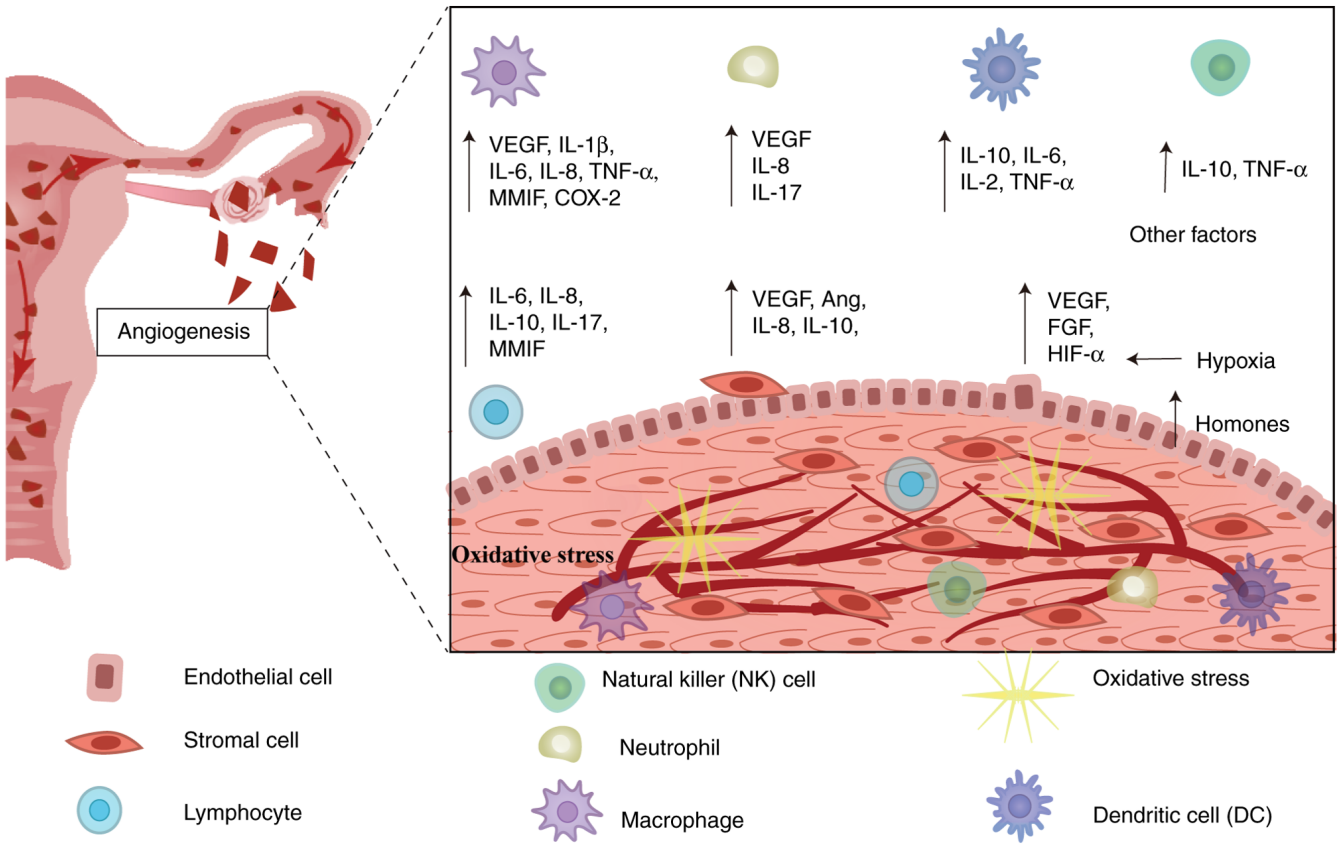

Figure 1. Angiogenic microenvironment of EM based on Sampson's retrograde menstruation theory, in which viable endothelial cells reflux into the peritoneal cavity. Under peritoneal hypoxia and altered immuno-inflammatory microenvironment, defective immune surveillance occurs, leading to imbalance of immune cells and secretion of relevant cytokines, which promotes ectopic endothelial colonization, adhesion and neovascularization. Ang, angiopoietin; IL, interleukin; FGF, fibroblast growth factor; MMIF, macrophage migration inhibitory factor; VEGF, vascular endothelial growth factor; COX-2, cyclooxygenase 2; TNF-α, tumor necrosis factor-α.

Table I. Expression of pro-angiogenic factors in intimal tissue, peritoneal fluid or serum/plasma of patients with EM.

Factor	Source	Test sample	(Refs.)
VEGF	Endometrial glandular epithelial and stromal cells, macrophages, neutrophils	Intimal tissue, serum, peritoneal fluid	(10,21,24,26,50)
FGF	Stromal cells, macrophages	Intimal tissue	(10)
Ang	Endothelial cells	Serum	(27)
HIF-1α	Stromal cells	Serum	(24)
IL-1β	Macrophages, monocytes	Peritoneal fluid	(20)
		Serum	(26,27)
IL-6	Macrophages, mast cells, lymphocytes	Peritoneal fluid	(21,23)
		Serum	(104)
IL-8	Endothelial cells, macrophages, neutrophils	Peritoneal fluid	(22)
		Serum	(22,26,27)
IL-10	Plasma cells, dendritic cells, NK cells	Serum	(26)
IL-17	Lymphocytes, neutrophils	Peritoneal fluid	(23)
		Serum	(23)
TNF-α	Macrophages, NK cells	Intimal tissue	(25)
		Serum	(26,27)
MMIF	Lymphocytes, macrophages	Serum	(24)
COX-2	Macrophages	Serum	(26)

VEGF, vascular endothelial growth factor; FGF, fibroblast growth factor; Ang, angiopoietin; NK, natural killer; HIF-1α, hypoxia-inducible factor-1α; IL, interleukin; TNF-α, tumor necrosis factor-α; MMIF, macrophage migration inhibitory factor; COX-2, cyclooxygenase 2.

stimulus that induces pathogenic polarization of macrophages towards the M2 phenotype (42). This suggests a synergistic role of inflammation and the Th17 immune response.

Molecules involved in angiogenesis in EM. Previous studies have found numerous similarities between EM angiogenesis and tumor pathologic angiogenesis (8,43). Ectopic endometrial tissue initially has a degree of hypoxia comparable with that of cells in growing tumor centers (16,44).

Hypoxia is one of the most potent stimuli for upregulation of angiogenic growth factors; it prevents proteasomal degradation of hypoxia-inducible factor-1α (HIF-1α) (44,45). HIF-1α is required for oxygen-regulated transcriptional activation of genes encoding VEGF to enhance hypoxia-induced angiogenesis. HIF-1α enters the nucleus to form hypoxia response elements and binds the promoter region of the VEGF gene, which in turn upregulates VEGF expression and promotes angiogenesis (9). In the hypoxic microenvironment of the peritoneal cavity, HIF-1α downregulates expression of chicken ovalbumin upstream of the promoter transcription factor II, which leads to elevated angiopoietin expression and promotes neovascularization of ectopic lesions in EM (46). Additionally, HIF-1α is involved in immune regulation and inflammatory responses and it can upregulate expression of IL-8 and COX-2, thus initiating IL-8- and COX-2-mediated angiogenic mechanisms and indirectly promoting ectopic endothelial neovascularization (47). The involvement of HIF-1α in regulating disease is complex and HIF-1α is also involved in cellular autophagy. HIF-1α promotes mesenchymal cell migration and invasion in EM via upregulation of autophagy (45). Reactive oxygen species (ROS) are a key element in stabilizing HIF-1α. The release of ROS and the expression of VEGF are enhanced under hypoxic conditions, which forms a positive feedback mechanism between ROS and VEGF in enhancing angiogenesis (48). As a consequence, HIF-1α is an important regulator that promotes angiogenesis and is involved in angiogenesis in EM via the complex regulation of multiple pathways.

VEGF is an important pro-angiogenic factor that induces vascular endothelial cell neogenesis and cell proliferation by binding to vascular endothelial cells, increases vascular permeability and promotes blood vessel formation (43,49). VEGF protein family includes VEGF-A, -B and -C, virus-encoded VEGF-D and placental growth factor, with VEGF-A playing pivotal roles in regulation of angiogenesis (43). The VEGF signaling pathway regulates activity of multiple kinases by binding to cell surface tyrosine kinase receptors, VEGF receptor (R)-1, VEGFR-2, and VEGFR-3, resulting in different biological effects that ultimately result in angiogenesis (43). In recent years, expression of VEGF has been studied in different experimental EM models and tissue samples from patients with EM (10,50-52). Numerous researchers have found that increased expression of VEGF in the serum and peritoneal fluid of patients with EM can serve as an auxiliary diagnostic indicator of EM (9,10,50). Li *et al* (10) found that angiogenic factors released from ESCs may be influenced by expression of fibrinogen α chain (FGA) and that the expression of pro-angiogenic factors, such as VEGF, platelet-derived growth factor (PDGF), FGF and MMP-2 and -9, is reduced in FGA-knockdown hEM15A cells. FGA may activate the VEGFA/VEGFR-2/FAK signaling pathway in EM and promote angiogenesis by regulating expression of VEGF-A and MMPs in EM ESCs. In addition, VEGF-C expression is upregulated in EM cells, and it has been demonstrated that VEGF-C enhances lymphangiogenic capacity of lymphatic endothelial cells via extracellular vesicle transport in an autograft mouse model of EM, whereas blocking the VEGF-C signaling pathway attenuates development of local chronic inflammation and EM (50). The expression of VEGF in EM is regulated by expression of multiple factors and related pathways and plays a vital regulatory role in the process of neovascularization in EM.

The stimulation of endometrial and endometriotic cells leads to activation of different intracellular pathways and associated signaling molecules. Nuclear factor-κB (NF-κB) is a transcription factor that mediates inflammatory signaling pathways and is a driver of inflammation and plays a crucial role in the development and regulation of inflammation (2). NF-κB is expressed in trace amounts in normal endometrium, but it is expressed at high levels in EM, suggesting that activated NF-κB serves an important role in regulating the development of ectopic endometrium (26,53). Gou *et al* (33) showed that estrogen receptor β (ERβ) regulates production of C-C motif chemokine ligand 2 through activation of the NF-κB signaling pathway in B cells, thereby recruiting macrophages to ectopic lesions in ESCs to promote pathogenesis. Additionally, ERβ stimulates expression of genes associated with the unfolded protein response in normal endometrium, inhibits the IL-6/JAK/STAT3 signaling pathway and suppresses the TNFα/NF-κB signaling pathway, leading to endometrial dysfunction associated with EM (54). In addition, oxidative stress is associated with development of EM and is a key inducer of the NF-κB signaling pathway in EM cells, extracellular high mobility group box-1 (HMGB-1), a prototypical molecule of damage-associated molecular patterns, inducing an inflammatory response via HMGB-1/TLR4/NF-κB axis (2,53). Excessive production of ROS in the pelvis of patients with EM is an important inducer of NF-κB-mediated chronic inflammatory responses, and NF-κB activation is primarily regulated by ROS, regulating the expression of cytokines, such as IL-10, in EM by activating the NF-κB pathway (26). Oxidative damage to DNA in EM increases DNA fragmentation and activates NF-κB signaling to promote transcription and expression of inflammatory factors such as TNF-α, and IL-1, -8 and -6 (26,55), while NF-κB is activated by TNF-α, IL-1β and LPS (56), thus creating positive feedback to promote alteration of the abdominal inflammatory microenvironment and the development of ectopic endothelial lesions. Additionally, the NF-κB signaling pathway decreases expression of antioxidant enzymes by activating the nitric oxide synthase (NOS)/NO signaling pathway, which is involved in oxidative stress (53).

In addition to VEGF, other factors have been shown to be involved in angiogenesis in EM. COX-2 serves as a rate-limiting enzyme for prostaglandins (PGs), induces the production of PGE2 and E2, which increase VEGF expression (57). COX-2 is rapidly upregulated in response to proinflammatory and pathogenic stimuli, and it is able to induce VEGF synthesis upon stimulation by cytokines (26,57) Furthermore, COX-2 has been shown to serve a vital role in the pathological process of diseases such as endometrial carcinoma and endometrial carcinoma (53,58). COX-2, which is either not expressed or

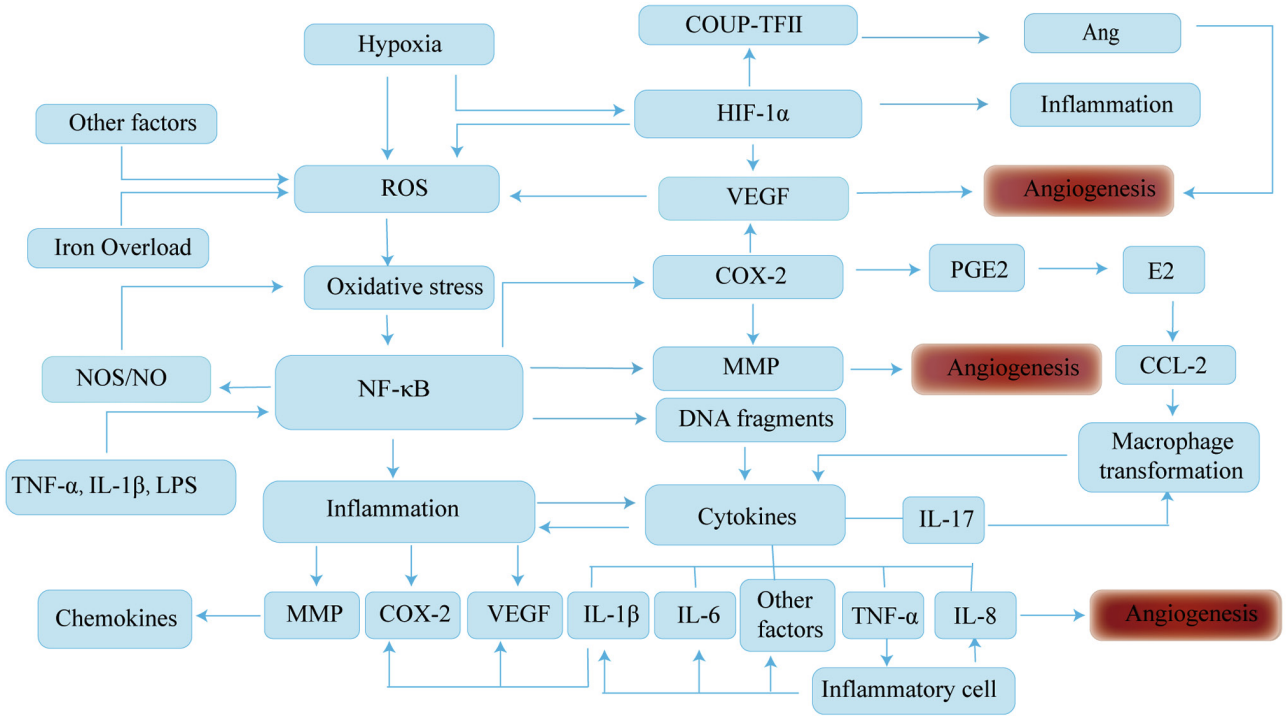

Figure 2. Molecular pathways of angiogenic signaling in EM. Angiogenesis is associated with a variety of factors, including abdominal microenvironment and immunomodulatory imbalance. In hypoxic conditions, ROS release and VEGF expression are enhanced. ROS can induce oxidative stress, which drives the activation of genes downstream of NF-κB signaling, induces inflammatory responses and regulates the expression of cytokines such as IL-8 and COX-2, which regulates angiogenesis. In addition, there is a positive feedback mechanism between ROS and VEGF, which contributes to angiogenesis. The interaction of the inflammatory response with cytokines can mediate differentiation of immune cells, which in turn exacerbates imbalance of the abdominal microenvironment and angiogenesis of the ectopic endothelium. EM, endometriosis; ROS, reactive oxygen species; VEGF, vascular endothelial growth factor; NF-κB, nuclear factor-κB; IL, interleukin; COX-2, cyclooxygenase 2; COUP-TFII, COUP transcription factor 2; Ang, angiopoietin; HIF-1α, hypoxia-inducible factor-1α; PGE2, prostaglandin E2; NOS, nitric oxide synthase; MMP, matrix metalloproteinase; CCL-2, C-C motif chemokine ligand 2; TNF-α, tumor necrosis factor-α; LPS, lipopolysaccharide.

expressed at low levels in normal endometrium, is aberrantly expressed in patients with EM and may regulate VEGF to serve a role in the process of disease development (54,57). MMPs play a key role in various pathophysiological processes, such as adhesion and invasion of ectopic endothelium (13,59). Furthermore, COX-2 can regulate angiogenesis via regulation of MMP-2 activity in EM by the COX-2/PGE2/phosphorylated AKT axis (60). Blocking the expression of COX-2 and/or AKT inhibits MMP-2 activity and endothelial tube formation and inhibition of MMP-2 and COX-2 notably decreases the number of lesions in a mouse model of EM (60).

In conclusion, the pathogenesis of EM is complex and its angiogenesis is driven by a variety of cytokines mediating pro- and anti-angiogenic effects, such as hormonal, immune and inflammatory oxidative stress. These cytokines interact with each other to form a complex network of regulatory mechanisms and are involved in development of neovascularization in EM via multiple cellular pathways (Fig. 2). Further studies on pathogenesis of EM will contribute to identification of biomarkers or biomarker groups to improve and the diagnostic process in a non-invasive manner.

4. New non-invasive biomarkers in EM

At present, reliable laboratory biomarkers for EM pathology are difficult to obtain and there are no uniform international standards (1). The gold standard for diagnosis of EM remains the pathological findings following surgical treatment (61,62). There is often a 6-12-year hiatus between onset and diagnosis of EM, with the delay being caused by multiple factors, including economic deprivation and uneven distribution of health services (63,64). Reliable biomarkers found in the biological fluids of affected patients may be an expedient diagnostic tool for EM, which would also facilitate an objective assessment of treatment efficacy.

Although lacking both specificity and sensitivity for this pathology, the most representative glycoproteins used as biomarkers for EM include cancer antigen CA-125 and CA-199, which have similar specificity and reflect the severity of disease (65,66). However, in total laparoscopic ectopic lesion removal, high CA-199 expression is markedly associated with a high postoperative recurrence rate; monitoring the expression of CA-199 may help predict the progression of EM (67).

Vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1) are members of the integrin adhesion protein family, expressed by endothelial and other cells, and are involved in inflammatory responses, immunity, tumor immune escape and other processes (68,69), potentially due to involvement of the NF-κB pathway in TNF-α-induced upregulation of ICAM-1 and VCAM-1 in vascular endothelial cells (70,71). Kuessel *et al* (72) showed that the mRNA levels of both VCAM-1 and ICAM-1 are high in normal peritoneal samples of patients with EM and that serum soluble VCAM-1 (sVCAM-1) levels are not influenced by the

Table II. Studies reporting the sensitivity and specificity of dysregulated miRNAs in EM.

miRNA	Sensitivity, %	Specificity, %	Alteration	(Refs.)
miRNA-125b-5p	100.0	96.0	↑	(74)
miRNA-34a-5p	79.0	49.0	↓	(95)
miRNA-122	96.5	94.1	↑	(86)
miRNA-141	71.9	70.8	↓	(94)
miRNA-185-5p	81.2	90.0	↓	(78)
miRNA-199a	100.0	100.0	↑	(86)
miRNAs-199b-3p	96.0	80.0	↑	(99)
miRNA-200a	90.6	62.5	↓	(94)
miRNA-200c	100.0	96.0	↑	(95)
miRNA-224-5p	84.0	80.0	↓	(99)
miRNA-342	90.0	91.2	↑	(79)
miRNA-451a	85.4	84.6	↑	(84)
miRNA-3613	92.7	61.0	↓	(79)
let-7d	83.3	100.0	↓	(80)
miRNA-199a, miRNA-122, miRNA-145 and miRNA-542-3p	93.2	96.0	-	(98)
miRNAs-199b-3p, miRNA-224-5p and let-7d-3p	96.0	100.0	-	(99)
miRNA-155, miRNA574-3p and miRNA139-3p	83.0	51.0	-	(97)

miRNA, microRNA.

entity of the lesion, the stage of menstrual cycle or the severity of the disease. The aforementioned study further indicated that the specificity and sensitivity of serum VCAM-1 for diagnosis of EM is 80 and 84%, respectively. It is noteworthy that the diagnostic specificity and sensitivity of sVCAM-1/sICAM-1 ratio, which further improved this predictive performance, were 86.7 and 90.3%, respectively. In addition, elevated levels of sICAM-1 may impair natural killer cell activity, which in turn accelerates the progression of EM (70).

VEGF, one of the most potent pro-angiogenic factors, is expressed at elevated levels in patients with EM and may be a potential biological molecule for the diagnosis of EM (10,50). A previous study demonstrated that degree of VEGF elevation is associated with the stage of EM, with additional marked elevation in advanced stages (24).

Serum microRNA (miRNA/miR) is a non-coding RNA consisting of 21-23 nucleotides widely found in eukaryotes, which bind exosomes or to specific protein complexes to protect against endogenous RNase degradation, playing an active role in the regulation of gene expression and cell cycle (73,74). Several studies (75,76) have shown that multiple miRNAs regulate angiogenesis and inflammatory responses in the ectopic endometrium by regulating expression of molecules such as VEGF, MMPs, IL and TGF-β1. Consequently, dysregulation of their expression serves an essential role in the pathogenesis of EM (75,77). Compared with conventional ultrasound, miRNAs have the advantages of improved stability and specificity, simpler detection methods and lower detection costs, they are becoming potential molecular indicators for non-invasive identification of EM (Table II).

An increasing number of studies have been conducted to detect expression of one or more specific miRNAs in plasma by reverse transcription-quantitative PCR to investigate their diagnostic value in EM and it has been hypothesized that the miR-125b, -451 and let-7 families may serve as potential circulating biomarkers for EM (78-80). A previous study showed that serum miR-125b-5p has a sensitivity and specificity of 100 and 96%, respectively, for the diagnosis of EM (74). In patients with EM, upregulation of miR-125b-5p and downregulation of let-7b-5p expression may be associated with an increase in cytokines such as TNF-α and IL-1β and -6 (81,82). These cytokines are hypothesized to be important components involved in angiogenesis (31,39). Migration inhibitory factor (MIF) is a pleiotropic inflammatory cytokine with upstream regulatory roles in immunity and has been shown to be involved in the development of EM. miRNA-451, which is hypothesized to target MIF, is a mitogenic cytokine that creates a proliferative and angiogenic phenotype for growth of ectopic endothelium (76). Compared with the healthy population, miRNA-451 expression is decreased in patients with endometrial co-infertility, suggesting that miRNA-451 expression levels are negatively associated with co-infertility in patients with EM and may be used as a marker for disease prognosis (83,84). In addition, elevated miR-145-5p expression levels in EM are associated with upregulation of VEGF-A and decreased levels of epidermal growth factor 2, phosphatase and tensin homolog and C-X-C chemokine receptor type 4 (75).

MiR-199a is another possible suitable biomarker for EM. miR-199a downregulates the expression of VEGF-A in ESCs under hypoxic conditions and partially attenuates angiogenesis in hematopoietic stem cells under hypoxic conditions by inhibiting the HIF-1α/VEGF-A pathway (85). Maged *et al* (86) showed that serum miR-199a and -122 have high sensitivity and specificity and miR-199a has 100% sensitivity and specificity for the diagnosis of EM. Another study showed that VEGF-A is a direct and functional target of miR-199a-5p and elevated miR-199a-5p expression inhibits the proliferation and angiogenesis of MSCs, as confirmed *in vitro* experiments and EM female C57BL/6j mouse models (87). Notably, HIF-1 upregulates miR-20a; miR-20a not only increases the expression of the VEGF-A angiogenic gene, but also downregulates anti-angiogenic thrombospondin 1 to promote angiogenesis (76,88-90). However, miR-20 as a biomarker for the diagnosis of EM remains to be investigated. In addition, dysregulation of miRNA-202-3p (91), miRNA-126 (92), miRNA-200 (75,93-95) and other genes mediate VEGF expression to promote angiogenesis and invasion of ectopic endothelium by promoting cell proliferation and angiogenesis. The aforementioned studies suggest that epigenetic abnormalities and dysregulation of miRNAs may play a key role in the formation of EM by affecting different physiological processes, which may also be beneficial for further studies on mechanisms of EM.

With the progress of miRNA research, diagnostic value of miRNAs has been further confirmed in the clinical setting. Moustafa *et al* (79) first demonstrated in a prospective study that plasma miRNAs accurately distinguish EM from other gynecological diseases, and miR-125b-5p, -150-5p, -342-3p and 451a are notably higher in patients with EM, while miR-3613-5p and let-7b are expressed at lower levels, miRNA expression levels are not markedly associated with menstrual cycle or hormonal drug use. To improve the diagnostic value of miRNA, co-diagnostic methods have been applied (96-99).

Results of several studies remain controversial and even contradictory due to the irreproducible nature of the studies (12,100). At present, no single or groups of miRNA biomarkers has sufficient specificity and sensitivity in the diagnosis of EM (101). Future studies need to adopt uniform and standardized methods to clarify the value of miRNA as a biological marker for early diagnosis and prognosis prediction of EM and for clinical translation and application.

The Internet of Medical Thing (IoMT) is the most emerging era of the Internet of Things (102,103). IoMT can generate large amounts of data without human intervention through connected smart medical devices, allowing healthcare professionals to facilitate disease detection by learning complex models and extracting meaningful information from large amounts of data (103). Based on this, researchers have trained on pulmonary embolism detection datasets and obtained satisfactory results in terms of sensitivity and specificity (102). To the best of our knowledge, however, its application in EM has not been reported yet. EM is a chronic inflammatory disease and using IoMT to establish a safe and effective system may contribute to the examination and treatment of the disease.

Numerous studies reveal (69,104,105) the importance and effectiveness of extracting various putative biomarkers from the biological fluids of affected patients. Nevertheless, due to the large heterogeneity between different studies, there is no uniform conclusion and further studies with larger sample sizes are needed to identify sensitive and specific indicators for transition from the laboratory to the clinic. As vascular mechanisms of ectopic endometrium are refined, newer and more accurate diagnostic markers for EM are expected to be discovered.

5. Anti-angiogenic treatment in EM

The current medical treatment for EM focuses on either hormonal modulation to induce a low estrogen state or surgical treatment to remove the ectopic lesions. However, even if the ectopic lesions are removed by surgery, certain patients will still have recurrence and even face the possibility of reoperation (106). Nevertheless, targeted therapeutic strategies based on anti-angiogenic therapy have been demonstrated in oncology and ophthalmology and have been widely used in clinical practice (8,43). As aforementioned, angiogenesis serves a key role in the development of EM and is essential for survival of ectopic endothelial implants. This shows that inhibition of ectopic endothelial angiogenesis is an important method to treat EM and if the mechanism can be regulated or inhibited or its pathway expression blocked, ectopic endothelial angiogenesis can be inhibited, improving the symptoms of patients and having value for clinical treatment. Currently, the primary anti-angiogenic drugs used in targeted therapy include anti-VEGF antibodies, VEGFR tyrosine kinase and COX-2 inhibitors and dopamine agonists (D2-ags; Table III).

Anti-VEGF and its receptor signaling pathway. Since VEGF is the most potent angiogenic factor and has an important role in EM (24), VEGF and its signaling pathway are considered to be the most effective targets for anti-angiogenic therapy, and in treatment of kidney, lung, rectal and cervical cancer (13,107). Bevacizumab and ranibizumab are monoclonal antibodies that bind and selectively neutralize VEGF activity by inhibiting binding of VEGF to VEGFR, primarily VEGFR2 or kinase insertion domain receptor, thereby reducing angiogenesis; additionally, both antibodies are effective against EM (51,52). Blocking VEGF signaling and inhibiting tyrosine kinase activity are potential targets for anti-angiogenic therapy (107-109). Research on VEGFR tyrosine kinase inhibitors has been ongoing and tyrosine kinase inhibitors such as sorafenib and sunitinib have been shown to be effective against EM (108,109). In comparing the effects of pazopanib, sorafenib and sunitinib on the VEGF/VEGFR protein kinase pathway and their role in EM, Yildiz *et al* (109) noted that pazopanib is more effective than control and other treatments, reducing EM lesions by ≥45%, but sorafenib exhibited improved modulation of VEGF. Anlotinib is a novel oral multitarget tyrosine kinase inhibitor developed independently in China that can effectively inhibit VEGFR, platelet-derived growth factor receptor, FGFR and c-Kit and exert antitumor angiogenesis effects and has been applied in gynecological tumors such as ovarian cancer; to the best of our knowledge however, no studies have reported on its application in EM (107).

D2-ags. E-MSCs express D2, with notably higher levels of ectopic endometrial expression relative to normal endometrial tissue (110). D2-ags decrease tumor size by targeting abnormal

Table III. Research progress of anti-angiogenic drugs in EM.

Class of drug	Drug	Experimental design	Mechanism of action	Outcome	(Refs.)
Anti-VEGF antibody	Bevacizumab	Rat model	Anti-VEGF	Significant decrease in lesion area	(52)
	Ranibizumab	Rat model	Anti-VEGF	Significant decrease in lesion area	(51)
Tyrosine kinase inhibitor	Sorafenib	Mouse model	Inhibition of VEGF	Decreased lesion implantation	(109)
	Sunitinib	Mouse model	Promotes maturation of peritoneal fluid MDSCs and suppresses immunosuppressive function	Significant decrease in the size and weight of EM lesions	(108)
	Pazopanib	Rat model	Inhibits VEGF and CD117 expression	Decreased lesion implantation	(109)
Dopamine receptor agonist	Cabergoline	Clinical trial	Inactivates VEGFR-2 to exert anti-angiogenic effects	Significant decrease in size of endometriomas	(112)
	Quinagolide	*In vitro*	Inhibition of AKT signaling pathway	Significant inhibition of ectopic E-MSC	(110)
COX-2 Inhibitor	Celecoxib	BALB/c mouse model	Inhibition of COX-2 signaling pathway	Decreased lesion implant volume and vascular density	(114)
	Parecoxib	C57BL/6 mouse model	Inhibition of COX-2 signaling pathway	Decreased volume of diseased implant volume	(117)
PPARγ activator	Rosiglitazone	BALB/c mouse and rat model	Activation of PPARγ signaling pathway	Inhibited lesion growth, cell proliferation and vascularization; increased apoptosis	(114,115)
Angiotensin II receptor blocker	Telmisartan	C57BL/6 mouse model	Combined blockade of AT1R and activation of PPARγ	Significant inhibition of the growth of lesions and decreased density of blood vessels	(116,117)
NF-κB inhibitor	BAY11-7085	*In vitro*	Inhibition of NF-κB signaling pathway and expression of anti-apoptotic proteins	Inhibition of the viability of ectopic endothelial cells	(118)
	Pyrrolidine dithiocarbamate	*In vitro*	Inhibition of NF-κB signaling pathway	Inhibition of COX-2 expression, decreased PGE2 production, inhibition of EM cell proliferation, angiogenesis and inflammatory response	(119)
Other	Ginsenoside Rg3	*In vitro*	Regulation of apoptosis and angiogenesis via nuclear factor/NF-κB signaling pathway	Significantly decreased levels of VEGF	(120)
	Curcumin	*In vitro*	Inhibition of NF-κB pathway activation	Decreased secretion of chemokines and cytokines	(121,122)
	Nobiletin	C57BL/6 mouse model	Inhibition of NF-κB pathway activation	Significantly decreased lesion size and pain in EM mice	(123)
	Dienogest	Clinical trial	Inhibition of NF-κB pathway	Effective decrease in endometrial tumor size and EM-associated pain	(124)

Table III. Continued.

Class of drug	Drug	Experimental design	Mechanism of action	Outcome	(Refs.)
Immunomodulator	Etanercept	Wistar Albino rat model	Decreased expression and activity of serum VEGF, IL-6 and TNF-α	Effective decrease in the volume of ectopic lesions	(125)
	Rapamycin	Mouse model	Inhibition of VEGF expression	Significant decrease in the volume of ectopic lesions	(126)
	Interleukin (IFN)	*In vitro*	Interference with the cell cycle	Inhibition of ESC cell proliferation and migration	(128)
Antioxidant	Melatonin	Clinical trial	Antioxidation	Improved patient sleep quality and decreased pain associated with EM	(129,131)
	Vitamins E and C	Clinical trial	Antioxidation	Decreased inflammatory markers in peritoneal fluid and chronic pelvic pain	(130)
	Resveratrol	Clinical trial	Antioxidation	Decreased expression levels of VEGF and TNF-α	(25)
Iron death inducer	Erastin	C57BL/6 mouse model	Induces ectopic endometrial stromal cell death	Significant decrease in ectopic lesions	(133)

VEGF, vascular endothelial growth factor; MDSC, myeloid-derived suppressor cells; EM, endometriosis; VEGFR, VEGF receptor; COX-2, cyclooxygenase 2; E-MSC, endometrial mesenchymal stromal cell; PPARγ, peroxisome proliferator-activated receptor γ; AT1R, angiotensin II type 1 receptor; TNF-α, tumor necrosis factor-α.

angiogenesis in pathological tissue, showing that D2-ags could be used to treat EM (111,112). Cabergoline, a dopamine agonist, exerts anti-angiogenic effects by inducing endocytosis of VEGFR-2 in endothelial cells, leading to decreased and inactivated VEGF-VEGFR-2 binding (112). D2-ags are as powerful as standard anti-angiogenic compounds in interfering with angiogenesis and lesion size (111,113). In addition, in a prospective clinical trial, D2-ags were shown to be superior to luteinizing hormone-releasing hormone agonists in decreasing size of endometrial tumors, with fewer drug side effects, easier administration and lower price (112). Quinagolide is a non-ergot-derived D2-ag that has been reported to reduce or eliminate peritoneal EM lesions in patients with EM (110). Another study found notable inhibition of E-MSCs by quinagolide, which decreases invasion and endothelial differentiation via the AKT signaling pathway, further supporting the theoretical basis for the use of this drug in treatment of EM (110). The role of quinagolide in EM is currently undergoing phase 2 clinical trials (trial nos. NCT03749109 and NCT03692403), which are expected to provide a novel treatment strategy for the future treatment of EM (110).

COX-2 inhibitor. Celecoxib, a potent COX-2 inhibitor, has been shown to inhibit EM lesions by markedly decreasing the size of ectopic lesions and vascular density in a study exploring the effects of celecoxib and rosiglitazone on implantation and growth of EM-like lesions in mice with EM (114). Additionally, treatment with peroxisome proliferator-activated receptor γ (PPARγ) activator rosiglitazone has also been shown to inhibit the growth of EM implants, and the combination of celecoxib and rosiglitazone is more potent than single application of celecoxib in the inhibition of ectopic EM lesions (114,115). Telmisartan, a partial agonist of PPARγ, also blocks angiotensin II type 1 receptor (AT1R); combined blockade of AT1R and activation of PPARγ markedly inhibits angiogenesis and growth in EM-like lesions in mice (116). In addition, Nenicu *et al* (117) found that combination of telmisartan and parecoxib in the treatment of endometrioid lesions increases the rate of lesion regression and notably improves therapeutic effects compared with treatment with telmisartan alone. This suggests that the combination of ≥2 drugs may achieve more desirable therapeutic effects than a single drug against angiogenesis.

NF-κB inhibitor. NF-κB, a key factor in signaling, can regulate growth of ectopic endothelium through multiple pathways (53). Therefore, NF-κB is considered an important target for anti-angiogenic therapy. BAY11-7085, an NF-κB inhibitor, inhibits the viability of EM cells and induces apoptosis in endometriotic cyst stromal cells by inhibiting anti-apoptotic proteins in an *in vitro* experimental study; its effect on normal endometrial cells is not notable, but, to the best of our knowledge, clinical studies for its treatment have not been reported (118). Pyrrolidine dithiocarbamate is another potent NF-κB inhibitor that inhibits NF-κB signaling in EM cells, suppresses COX-2 expression, decreases PGE2 production and suppresses EM cell proliferation, angiogenesis and inflammatory responses (119). In addition, natural extracts such as ginsenoside Rg3 and curcumin decrease EM by regulating apoptosis and inhibiting VEGF expression and angiogenesis via the NF-κB signaling pathway (120-122). The low risk of adverse effects of these

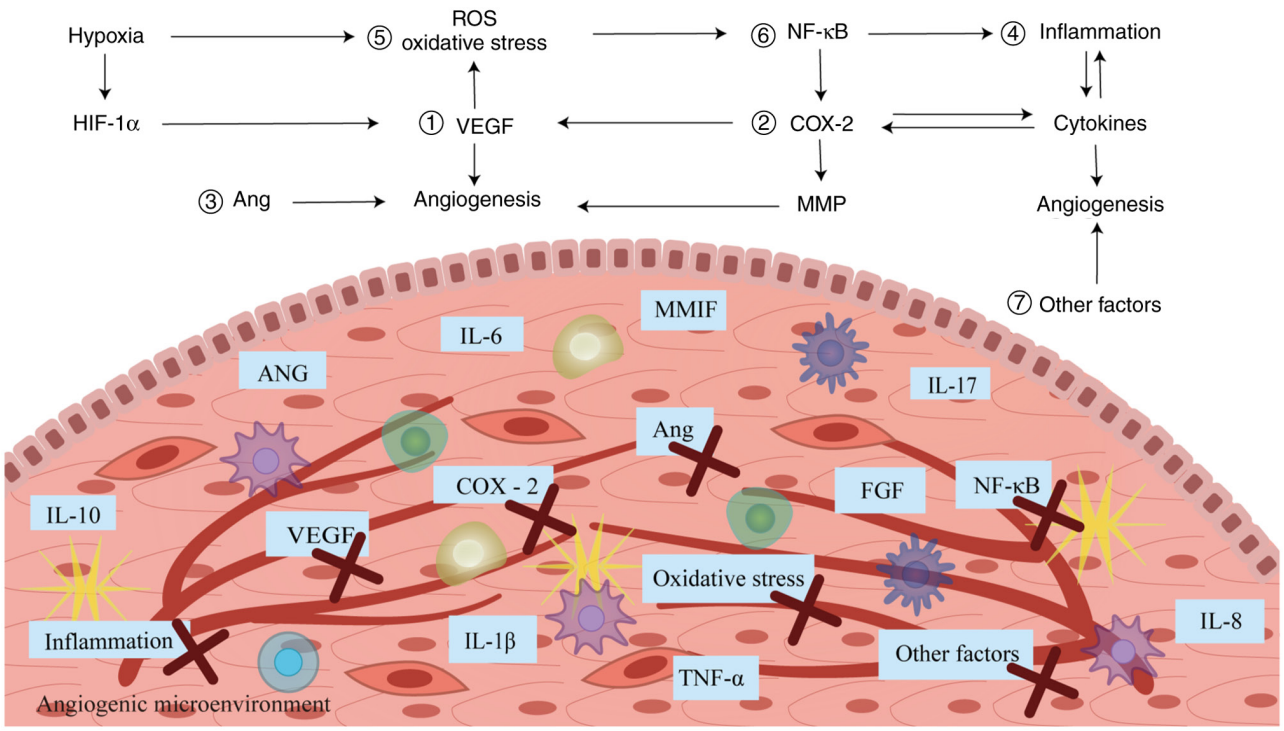

Figure 3. Basis of action of anti-angiogenic drugs in EM. (1) Anti-VEGF drugs such as bevacizumab and sorafenib. (2) COX-2 inhibitors such as celecoxib and parecoxib. (3) Angiotensin II receptor blockers such as telmisartan. (4) Immunomodulators such as etanercept and rapamycin. (5) Antioxidants such as melatonin and resveratrol. (6) NF-κB inhibitors such as BAY11-7085 and pyrrolidine dithiocarbamate. (7) Other drugs such as cabergoline and quinagolide. EM, endometriosis; VEGF, vascular endothelial growth factor; COX-2, cyclooxygenase 2; NF-κB, nuclear factor-κB; IL, interleukin; ANG, angiotensin; TNF-α, tumor necrosis factor-α; MMIF, macrophage migration inhibitory factor; Ang, angiopoietin; FGF, fibroblast growth factor; HIF-1α, hypoxia-inducible factor-1α.

natural products indicates their potential clinical value in the treatment of EM. It has been demonstrated that the inhibitory effect of nobiletin on EM is achieved by inhibiting activation of the NF-κB pathway, which markedly decreases the regulation of the expression of angiogenic factors, including VEGF and E-cadherin, in ectopic endometrium (123). Dienogest is an artificially developed, fourth-generation progestin with strong anti-proliferative effects on EM implants, as well as anti-angiogenic and anti-inflammatory properties (124). Its mechanism of action may be associated with inhibition of the NF-κB pathway, which is effective in decreasing the size of endometriomas and EM-related pain and has a good safety and tolerability profile, with improved clinical efficacy in young patients with endometriomas who have not yet had children (124). Moreover, 2-cyano -3,12-dioxooleana1,9-dien-28-oic acid effectively inhibit EM by increasing ectopic cell apoptosis and decreasing angiogenesis by modulating Nrf2 and NF-κB pathways and has anti-fibrotic, anti-inflammatory and antioxidant effects in EM (55).

Immunomodulators. Numerous researchers have noted involvement of immune inflammatory factors in ectopic endothelial vascularization (18,27,104). Therefore, modulation of the immune system may also serve a role in EM treatment. Etanercept, a fusion protein consisting of the human recombinant soluble TNF receptor 2 bound to human Fc antibody subunits, is effective in decreasing the volume of ectopic lesions in rats by decreasing serum VEGF and IL-6 levels, and TNF-α activity (125). An experiment investigating the effect of rapamycin (RAPA) on EM lesions in severe combined immunodeficient mice found that RAPA inhibits the growth of EM lesions, potentially by suppressing expression of VEGF in the lesions and thus angiogenesis (126). In addition, similar pharmacological efficacy of interferons (IFNs) and pentoxifylline for treatment of EM has been observed, IFN-β 1a has a notably stronger *in vitro* inhibitory effect on ESC proliferation and migration than IFN-α 2b, while the efficacy and safety of pentoxifylline in treatment of EM has been reported, but there is insufficient evidence to support its effectiveness in the treatment of infertility and pain in EM (127,128). The data from the aforementioned studies provide a theoretical basis for future clinical trials.

Antioxidant therapy. With in-depth research on development and targets of EM, the important role of oxidative stress in EM has become increasingly recognized (2,53). In parallel, studies have demonstrated that antioxidants inhibit the development of ectopic endothelium and achieve efficacy in the treatment of EM (25,129-131). The effects of antioxidant melatonin and vitamins E and C on EM are all demonstrated in clinical randomized placebo-controlled trials; they notably improve the reduction of chronic pelvic pain and decrease expression of inflammatory markers in peritoneal fluid in patients with EM (129-132). Resveratrol is a naturally occurring synthetic polyphenolic compound with antitumor, anti-inflammatory, antioxidant and anti-angiogenic properties (25). In a randomized controlled clinical trial study, resveratrol was found to decrease angiogenesis and inflammation in endometrial tissue of patients with EM by downregulating expression of VEGF and TNF-α (25). Although melatonin, resveratrol and combined vitamin C and E supplements have shown good results in treatment of EM, their use requires further investigation. Recently, Li *et al* (133) demonstrated that the iron death

inducer erastin could induce ectopic endometrial stromal cell death in C57BL/6 female mouse model of EM, and the ectopic lesions are reduced after treatment with erastin, suggesting that erastin may be a potential drug for treatment of EM, which provides a new idea for the targeted treatment of EM.

In conclusion, anti-angiogenic therapy has become a focal point of medical research and has an improved effect in the treatment of EM, which may provide a potential novel treatment for EM (Fig. 3). However, most of the drug application research results are at the stage of *in vitro* and animal experiments; although some drugs are at the stage of clinical experiments, there is still lack of drug safety and efficacy assessment. Therefore, more clinical trials are needed to assess the value of these drugs clinically.

6. Conclusions

Although EM is a benign lesion, the mechanism of its angiogenesis has similarities with pathologic angiogenesis mediating tumor and metastasis, which is complicated by multiple factors and mechanisms. The improvement of understanding of the EM angiogenic network regulation system has brought new hope for its diagnosis and treatment. However, the majority of studies are still at the laboratory stage, and to the best of our knowledge, there are no satisfactory clinical trials due to differences in research data and non-reproducibility, making it challenging to apply non-invasive biomarkers and anti-angiogenic drugs in the clinic.

In addition, clinical evidence for the efficacy of anti-angiogenic treatment strategies in EM is lacking. Anti-angiogenic therapy may adversely affect normal physiological angiogenesis such as ovulation and wound healing (134,135). Research is required to elucidate the interactions between factors in the angiogenic microenvironment to discover more effective targets for drug therapy. In addition, clinical trials are needed to evaluate the therapeutic value of these serum markers and anti-vascular drugs and to strengthen multi-targeted combined diagnosis and treatment to inhibit angiogenesis.

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Availability of data and materials

Not applicable.

Authors' contributions

CB conceived the study, performed the literature review, wrote the manuscript and constructed figures. YW conceived and supervised the study and wrote and edited the manuscript. Both authors have read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Smolarz B, Szyłło K and Romanowicz H: Endometriosis: Epidemiology, classification, pathogenesis, treatment and genetics (Review of Literature). Int J Mol Sci 22: 10554, 2021.
2. Samimi M, Pourhanifeh MH, Mehdizadehkashi A, Eftekhar T and Asemi Z: The role of inflammation, oxidative stress, angiogenesis, and apoptosis in the pathophysiology of endometriosis: Basic science and new insights based on gene expression. J Cell Physiol 234: 19384-19392, 2019.
3. Zondervan KT, Becker CM and Missmer SA: Endometriosis. N Engl J Med 382: 1244-1256, 2020.
4. Brasil DL, Montagna E, Trevisan CM, La Rosa VL, Laganà AS, Barbosa CP, Bianco B and Zaia V: Psychological stress levels in women with endometriosis: Systematic review and meta-analysis of observational studies. Minerva Med 111: 90-102, 2020.
5. Sullivan-Myers C, Sherman KA, Beath AP, Duckworth TJ and Cooper MJW: Delineating sociodemographic, medical and quality of life factors associated with psychological distress in individuals with endometriosis. Hum Reprod 36: 2170-2180, 2021.
6. Wang Y, Nicholes K and Shih IM: The origin and pathogenesis of endometriosis. Annu Rev Pathol 15: 71-95, 2020.
7. Laganà AS, Vitale SG, Salmeri FM, Triolo O, Ban Frangež H, Vrtačnik-Bokal E, Stojanovska L, Apostolopoulos V, Granese R and Sofo V: Unus pro omnibus, omnes pro uno: A novel, evidence-based, unifying theory for the pathogenesis of endometriosis. Med Hypotheses 103: 10-20, 2017.
8. Dudley AC and Griffioen AW: Pathological angiogenesis: Mechanisms and therapeutic strategies. Angiogenesis 26: 313-347, 2023.
9. Ben Dhaou C, Mandi K, Frye M, Acheampong A, Radi A, De Becker B, Antoine M, Baeyens N, Wittamer V and Parmentier M: Chemerin regulates normal angiogenesis and hypoxia-driven neovascularization. Angiogenesis 25: 159-179, 2022.
10. Li H, Cai E, Cheng H, Ye X, Ma R, Zhu H and Chang X: FGA Controls VEGFA secretion to promote angiogenesis by activating the VEGFR2-FAK signalling pathway. Front Endocrinol (Lausanne) 13: 791860, 2022.
11. Tan Y, Flynn WF, Sivajothi S, Luo D, Bozal SB, Davé M, Luciano AA, Robson P, Luciano DE and Courtois ET: Single-cell analysis of endometriosis reveals a coordinated transcriptional programme driving immunotolerance and angiogenesis across eutopic and ectopic tissues. Nat Cell Biol 24: 1306-1318, 2022.
12. Hon JX, Wahab NA, Karim AKA, Mokhtar NM and Mokhtar MH: MicroRNAs in Endometriosis: Insights into inflammation and progesterone resistance. Int J Mol Sci 24: 15001, 2023.
13. Potente M, Gerhardt H and Carmeliet P: Basic and therapeutic aspects of angiogenesis. Cell 146: 873-887, 2011.
14. Cha J, Sun X and Dey SK: Mechanisms of implantation: Strategies for successful pregnancy. Nat Med 18: 1754-1767, 2012.
15. Tarokh M, Ghaffari Novin M, Poordast T, Tavana Z, Nazarian H, Norouzian M and Gharesi-Fard B: Serum and peritoneal fluid cytokine profiles in infertile women with endometriosis. Iran J Immunol 16: 151-162, 2019.
16. Laschke MW and Menger MD: Basic mechanisms of vascularization in endometriosis and their clinical implications. Hum Reprod Update 24: 207-224, 2018.

17. Symons LK, Miller JE, Kay VR, Marks RM, Liblik K, Koti M and Tayade C: The immunopathophysiology of endometriosis. Trends Mol Med 24: 748-762, 2018.
18. Chen S, Liu Y, Zhong Z, Wei C, Liu Y and Zhu X: Peritoneal immune microenvironment of endometriosis: Role and therapeutic perspectives. Front Immunol 14: 1134663, 2023.
19. Guo F, He Y, Fan Y, Du Z, Sun H, Feng Z, Zhang G and Xiong T: G-CSF and IL-6 may be involved in formation of endometriosis lesions by increasing the expression of angiogenic factors in neutrophils. Mol Hum Reprod 27: gaab064, 2021.
20. Sikora J, Mielczarek-Palacz A and Kondera-Anasz Z: Association of the precursor of interleukin-1β and peritoneal inflammation-role in pathogenesis of endometriosis. J Clin Lab Anal 30: 831-837, 2016.
21. Li C, Zhao HL, Li YJ, Zhang YY, Liu HY, Feng FZ and Yan H: The expression and significance of leukemia inhibitory factor, interleukin-6 and vascular endothelial growth factor in Chinese patients with endometriosis. Arch Gynecol Obstet 304: 163-170, 2021.
22. Barcz E, Różewska ES, Kaminski P, Demkow U, Bobrowska K and Marianowski L: Angiogenic activity and IL-8 concentrations in peritoneal fluid and sera in endometriosis. Int J Gynaecol Obstet 79: 229-235, 2002.
23. Sikora J, Smycz-Kubańska M, Mielczarek-Palacz A, Bednarek I and Kondera-Anasz Z: The involvement of multifunctional TGF-β and related cytokines in pathogenesis of endometriosis. Immunol Lett 201: 31-37, 2018.
24. Zhang F, Liu XL, Wang W, Dong HL, Xia YF, Ruan LP and Liu LP: Expression of MMIF, HIF-1α and VEGF in serum and endometrial tissues of patients with endometriosis. Curr Med Sci 38: 499-504, 2018.
25. Khodarahmian M, Amidi F, Moini A, Kashani L, Salahi E, Danaii-Mehrabad S, Nashtaei MS, Mojtahedi MF, Esfandyari S and Sobhani A: A randomized exploratory trial to assess the effects of resveratrol on VEGF and TNF-α 2 expression in endometriosis women. J Reprod Immunol 143: 103248, 2021.
26. Nanda A, K T, Banerjee P, Dutta M, Wangdi T, Sharma P, Chaudhury K and Jana SK: Cytokines, angiogenesis, and extracellular matrix degradation are augmented by oxidative stress in endometriosis. Ann Lab Med 40: 390-397, 2020.
27. Singh AK, Dutta M, Chattopadhyay R, Chakravarty B and Chaudhury K: Intrafollicular interleukin-8, interleukin-12, and adrenomedullin are the promising prognostic markers of oocyte and embryo quality in women with endometriosis. J Assist Reprod Genet 33: 1363-1372, 2016.
28. Monsanto SP, Edwards AK, Zhou J, Nagarkatti P, Nagarkatti M, Young SL, Lessey BA and Tayade C: Surgical removal of endometriotic lesions alters local and systemic proinflammatory cytokines in endometriosis patients. Fertil Steril 105: 968-977. e5, 2016.
29. Vazgiourakis VM, Zervou MI, Papageorgiou L, Chaniotis D, Spandidos DA, Vlachakis D, Eliopoulos E and Goulielmos GN: Association of endometriosis with cardiovascular disease: Genetic aspects (Review). Int J Mol Med 51: 29, 2023.
30. Ahn SH, Edwards AK, Singh SS, Young SL, Lessey BA and Tayade C: IL-17A contributes to the pathogenesis of endometriosis by triggering proinflammatory cytokines and angiogenic growth factors. J Immunol 195: 2591-2600, 2015.
31. Lin YJ, Lai MD, Lei HY and Wing LY: Neutrophils and macrophages promote angiogenesis in the early stage of endometriosis in a mouse model. Endocrinology 147: 1278-1286, 2006.
32. Yan WK, Liu YN, Song SS, Kang JW, Zhang Y, Lu L, Wei SW, Xu QX, Zhang WQ, Liu XZ, *et al*: Zearalenone affects the growth of endometriosis via estrogen signaling and inflammatory pathways. Ecotoxicol Environ Saf 241: 113826, 2022.
33. Gou Y, Li X, Li P, Zhang H, Xu T, Wang H, Wang B, Ma X, Jiang X and Zhang Z: Estrogen receptor β upregulates CCL2 via NF-κB signaling in endometriotic stromal cells and recruits macrophages to promote the pathogenesis of endometriosis. Hum Reprod 34: 646-658, 2019.
34. Laganà AS, Salmeri FM, Ban Frangež H, Ghezzi F, Vrtačnik-Bokal E and Granese R: Evaluation of M1 and M2 macrophages in ovarian endometriomas from women affected by endometriosis at different stages of the disease. Gynecol Endocrinol 36: 441-444, 2020.
35. Li Q, Yuan M, Jiao X, Huang Y, Li J, Li D, Ji M and Wang G: M1 macrophage-derived nanovesicles repolarize M2 macrophages for inhibiting the development of endometriosis. Front Immunol 12: 707784, 2021.
36. Vallvé-Juanico J, Houshdaran S and Giudice LC: The endometrial immune environment of women with endometriosis. Hum Reprod Update 25: 564-591, 2019.
37. Gao X, Gao H, Shao W, Wang J, Li M and Liu S: The extracellular vesicle-macrophage regulatory axis: A novel pathogenesis for endometriosis. Biomolecules 13: 1376, 2023.
38. Suen JL, Chang Y, Shiu YS, Hsu CY, Sharma P, Chiu CC, Chen YJ, Hour TC and Tsai EM: IL-10 from plasmacytoid dendritic cells promotes angiogenesis in the early stage of endometriosis. J Pathol 249: 485-497, 2019.
39. Fainaru O, Adini A, Benny O, Adini I, Short S, Bazinet L, Nakai K, Pravda E, Hornstein MD, D'Amato RJ and Folkman J: Dendritic cells support angiogenesis and promote lesion growth in a murine model of endometriosis. FASEB J 22: 522-529, 2008.
40. Talaat RM, Mohamed SF, Bassyouni IH and Raouf AA: Th1/Th2/Th17/Treg cytokine imbalance in systemic lupus erythematosus (SLE) patients: Correlation with disease activity. Cytokine 72: 146-153, 2015.
41. Kang YJ, Cho HJ, Lee Y, Park A, Kim MJ, Jeung IC, Jung YW, Jung H, Choi I, Lee HG and Yoon SR: IL-17A and Th17 cells contribute to endometrial cell survival by inhibiting apoptosis and NK cell mediated cytotoxicity of endometrial cells via ERK1/2 pathway. Immune Netw 23: e14, 2023.
42. Miller JE, Ahn SH, Marks RM, Monsanto SP, Fazleabas AT, Koti M and Tayade C: IL-17A modulates peritoneal macrophage recruitment and M2 polarization in endometriosis. Front Immunol 11: 108, 2020.
43. Apte RS, Chen DS and Ferrara N: VEGF in signaling and disease: Beyond discovery and development. Cell 176: 1248-1264, 2019.
44. Wu MH, Hsiao KY and Tsai SJ: Hypoxia: The force of endometriosis. J Obstet Gynaecol Res 45: 532-541, 2019.
45. Liu H, Zhang Z, Xiong W, Zhang L, Xiong Y, Li N, He H, Du Y and Liu Y: Hypoxia-inducible factor-1α promotes endometrial stromal cells migration and invasion by upregulating autophagy in endometriosis. Reproduction 153: 809-820, 2017.
46. Fu JL, Hsiao KY, Lee HC, Li WN, Chang N, Wu MH and Tsai SJ: Suppression of COUP-TFII upregulates angiogenin and promotes angiogenesis in endometriosis. Hum Reprod 33: 1517-1527, 2018.
47. Zhou Y, Jin Y, Wang Y and Wu R: Hypoxia activates the unfolded protein response signaling network: An adaptive mechanism for endometriosis. Front Endocrinol (Lausanne) 13: 945578, 2022.
48. Cheng J, Yang HL, Gu CJ, Liu YK, Shao J, Zhu R, He YY, Zhu XY and Li MQ: Melatonin restricts the viability and angiogenesis of vascular endothelial cells by suppressing HIF-1α/ROS/VEGF. Int J Mol Med 43: 945-955, 2019.
49. Ferrara N and Adamis AP: Ten years of anti-vascular endothelial growth factor therapy. Nat Rev Drug Discov 15: 385-403, 2016.
50. Li WN, Hsiao KY, Wang CA, Chang N, Hsu PL, Sun CH, Wu SR, Wu MH and Tsai SJ: Extracellular vesicle-associated VEGF-C promotes lymphangiogenesis and immune cells infiltration in endometriosis. Proc Natl Acad Sci USA 117: 25859-25868, 2020.
51. Ureyen Ozdemir E, Adali E, Islimye Taskin M, Yavasoglu A, Aktug H, Oltulu F and Inceboz U: Effects of ranibizumab and zoledronic acid on endometriosis in a rat model. Arch Gynecol Obstet 305: 267-274, 2022.
52. Zani ACT, Valerio FP, Meola J, da Silva AR, Nogueira AA, Candido-Dos-Reis FJ, Poli-Neto OB and Rosa-E-Silva JC: Impact of bevacizumab on experimentally induced endometriotic lesions: Angiogenesis, invasion, apoptosis, and cell proliferation. Reprod Sci 27: 1943-1950, 2020.
53. Liu Y, Wang J and Zhang X: An update on the multifaceted role of NF-kappaB in endometriosis. Int J Biol Sci 18: 4400-4413, 2022.
54. Shamloo N, Taghavi N, Yazdani F, Azimian P and Ahmadi S: Evaluation of VEGF expression correlates with COX-2 expression in pleomorphic adenoma, mucoepidermoid carcinoma and adenoid cystic carcinoma. Dent Res J (Isfahan) 17: 100-106, 2020.
55. Siracusa R, D'Amico R, Cordaro M, Peritore AF, Genovese T, Gugliandolo E, Crupi R, Impellizzeri D, Cuzzocrea S, Fusco R and Di Paola R: The Methyl Ester of 2-Cyano-3,12-Dioxooleana-1,9-Dien-28-Oic acid reduces endometrial lesions development by modulating the NFkB and Nrf2 pathways. Int J Mol Sci 22: 3991, 2021.
56. Santulli P, Marcellin L, Tosti C, Chouzenoux S, Cerles O, Borghese B, Batteux F and Chapron C: MAP kinases and the inflammatory signaling cascade as targets for the treatment of endometriosis? Expert Opin Ther Targets 19: 1465-1483, 2015.
57. Lai ZZ, Yang HL, Ha SY, Chang KK, Mei J, Zhou WJ, Qiu XM, Wang XQ, Zhu R, Li DJ and Li MQ: Cyclooxygenase-2 in Endometriosis. Int J Biol Sci 15: 2783-2797, 2019.

58. Hashemi Goradel N, Najafi M, Salehi E, Farhood B and Mortezaee K: Cyclooxygenase-2 in cancer: A review. J Cell Physiol 234: 5683-5699, 2019.
59. Ke J, Ye J, Li M and Zhu Z: The role of matrix metalloproteinases in endometriosis: A potential target. Biomolecules 11: 1739, 2021.
60. Jana S, Chatterjee K, Ray AK, DasMahapatra P and Swarnakar S: Regulation of matrix metalloproteinase-2 activity by COX-2-PGE2-pAKT axis promotes angiogenesis in endometriosis. PLoS One 11: e0163540, 2016.
61. Horne AW, Daniels J, Hummelshoj L, Cox E and Cooper KG: Surgical removal of superficial peritoneal endometriosis for managing women with chronic pelvic pain: time for a rethink? BJOG 126: 1414-1416, 2019.
62. Kiesel L and Sourouni M: Diagnosis of endometriosis in the 21st century. Climacteric 22: 296-302, 2019.
63. Kotowska M, Urbaniak J, Falęcki WJ, Łazarewicz P, Masiak M and Szymusik I: Awareness of endometriosis symptoms-A cross sectional survey among polish women. Int J Environ Res Public Health 18: 9919, 2021.
64. Ghai V, Jan H, Shakir F, Haines P and Kent A: Diagnostic delay for superficial and deep endometriosis in the United Kingdom. J Obstet Gynaecol 40: 83-89, 2020.
65. Rokhgireh S, Mehdizadeh Kashi A, Chaichian S, Delbandi AA, Allahqoli L, Ahmadi-Pishkuhi M, Khodaverdi S and Alkatout I: The diagnostic accuracy of combined Enolase/Cr, CA125, and CA19-9 in the detection of endometriosis. Biomed Res Int 2020: 5208279, 2020.
66. Harada T, Kubota T and Aso T: Usefulness of CA19-9 versus CA125 for the diagnosis of endometriosis. Fertil Steril 78: 733-739, 2002.
67. Zhang X, Nie D, Zhang L and Liu X: Study on diagnostic values and pathological conditions of serum HGF and CA199 in endometriosis. Am J Transl Res 13: 2849-2857, 2021.
68. Anastasiu CV, Moga MA, Elena Neculau A, Bălan A, Scârneciu I, Dragomir RM, Dull AM and Chicea LM: Biomarkers for the noninvasive diagnosis of endometriosis: State of the art and future perspectives. Int J Mol Sci 21: 1750, 2020.
69. Moein Mahini S, Younesi M, Mortazavi G, Samare-Najaf M, Karim Azadbakht M and Jamali N: Non-invasive diagnosis of endometriosis: Immunologic and genetic markers. Clin Chim Acta 538: 70-86, 2023.
70. Kim KH, Park JK, Choi YW, Kim YH, Lee EN, Lee JR, Kim HS, Baek SY, Kim BS, Lee KS and Yoon S: Hexane extract of aged black garlic reduces cell proliferation and attenuates the expression of ICAM-1 and VCAM-1 in TNF-α-activated human endometrial stromal cells. Int J Mol Med 32: 67-78, 2013.
71. Fukaya T, Sugawara J, Yoshida H, Murakami T and Yajima A: Intercellular adhesion molecule-1 and hepatocyte growth factor in human endometriosis: Original investigation and a review of literature. Gynecol Obstet Invest 47 (Suppl 1): S11-S16; discussion 16-17, 1999.
72. Kuessel L, Wenzl R, Proestling K, Balendran S, Pateisky P, Yotova I, Yerlikaya G, Streubel B and Husslein H: Soluble VCAM-1/soluble ICAM-1 ratio is a promising biomarker for diagnosing endometriosis. Hum Reprod 32: 770-779, 2017.
73. O'Brien J, Hayder H, Zayed Y and Peng C: Overview of MicroRNA biogenesis, mechanisms of actions, and circulation. Front Endocrinol (Lausanne) 9: 402, 2018.
74. Cosar E, Mamillapalli R, Ersoy GS, Cho S, Seifer B and Taylor HS: Serum microRNAs as diagnostic markers of endometriosis: A comprehensive array-based analysis. Fertil Steril 106: 402-409, 2016.
75. Yang RQ, Teng H, Xu XH, Liu SY, Wang YH, Guo FJ and Liu XJ: Microarray analysis of microRNA deregulation and angiogenesis-related proteins in endometriosis. Genet Mol Res 15: 2016.
76. Zubrzycka A, Migdalska-Sęk M, Jędrzejczyk S and Brzeziańska-Lasota E: Circulating miRNAs related to epithelial-mesenchymal transitions (EMT) as the new molecular markers in endometriosis. Curr Issues Mol Biol 43: 900-916, 2021.
77. Quintero-Fabián S, Arreola R, Becerril-Villanueva E, Torres-Romero JC, Arana-Argáez V, Lara-Riegos J, Ramírez-Camacho MA and Alvarez-Sánchez ME: Role of matrix metalloproteinases in angiogenesis and cancer. Front Oncol 9: 1370, 2019.
78. Hossein Razi M, Eftekhar M, Ghasemi N, Hasan Sheikhha M and Dehghani Firoozabadi A: Expression levels of circulatory mir-185-5p, vascular endothelial growth factor, and platelet-derived growth factor target genes in endometriosis. Int J Reprod Biomed 18: 347-358, 2020.
79. Moustafa S, Burn M, Mamillapalli R, Nematian S, Flores V and Taylor HS: Accurate diagnosis of endometriosis using serum microRNAs. Am J Obstet Gynecol 223: 557.e1-557.e11, 2020.
80. Cho S, Mutlu L, Grechukhina O and Taylor HS: Circulating microRNAs as potential biomarkers for endometriosis. Fertil Steril 103: 1252-1260.e1, 2015.
81. Sheikhvatan M, Chaichian S and Moazzami B: A systematic review and bioinformatics study on genes and micro-RNAs involving the transformation of endometriosis into ovarian cancer. Microrna 9: 101-111, 2020.
82. Nematian SE, Mamillapalli R, Kadakia TS, Majidi Zolbin M, Moustafa S and Taylor HS: Systemic inflammation induced by microRNAs: Endometriosis-Derived alterations in circulating microRNA 125b-5p and Let-7b-5p regulate macrophage cytokine production. J Clin Endocrinol Metab 103: 64-74, 2018.
83. Wang L, Zhang J, Sun H, Ji X and Zhang S: Effect of miR-451 on IVF/ICSI-ET outcome in patient with endometriosis and infertility. Am J Transl Res 13: 13051-13058, 2021.
84. Nothnick WB, Falcone T, Joshi N, Fazleabas AT and Graham A: Serum miR-451a levels are significantly elevated in women with endometriosis and recapitulated in baboons (Papio anubis) with experimentally-induced disease. Reprod Sci 24: 1195-1202, 2017.
85. Dai L, Lou W, Zhu J, Zhou X and Di W: MiR-199a inhibits the angiogenic potential of endometrial stromal cells under hypoxia by targeting HIF-1α/VEGF pathway. Int J Clin Exp Pathol 8: 4735-4744, 2015.
86. Maged AM, Deeb WS, El Amir A, Zaki SS, El Sawah H, Al Mohamady M, Metwally AA and Katta MA: Diagnostic accuracy of serum miR-122 and miR-199a in women with endometriosis. Int J Gynaecol Obstet 141: 14-19, 2018.
87. Hsu CY, Hsieh TH, Tsai CF, Tsai HP, Chen HS, Chang Y, Chuang HY, Lee JN, Hsu YL and Tsai EM: miRNA-199a-5p regulates VEGFA in endometrial mesenchymal stem cells and contributes to the pathogenesis of endometriosis. J Pathol 232: 330-343, 2014.
88. Lin SC, Wang CC, Wu MH, Yang SH, Li YH and Tsai SJ: Hypoxia-induced microRNA-20a expression increases ERK phosphorylation and angiogenic gene expression in endometriotic stromal cells. J Clin Endocrinol Metab 97: E1515-1523, 2012.
89. Lei Z, Li B, Yang Z, Fang H, Zhang GM, Feng ZH and Huang B: Regulation of HIF-1alpha and VEGF by miR-20b tunes tumor cells to adapt to the alteration of oxygen concentration. PLoS One 4: e7629, 2009.
90. Ramón LA, Braza-Boïls A, Gilabert-Estellés J, Gilabert J, España F, Chirivella M and Estellés A: microRNAs expression in endometriosis and their relation to angiogenic factors. Hum Reprod 26: 1082-1090, 2011.
91. Marí-Alexandre J, García-Oms J, Barceló-Molina M, Gilabert-Aguilar J, Estellés A, Braza-Boíls A and Gilabert-Estellés J: MicroRNAs and angiogenesis in endometriosis. Thromb Res 135 (Suppl 1): S38-S40, 2015.
92. van Solingen C, Seghers L, Bijkerk R, Duijs JM, Roeten MK, van Oeveren-Rietdijk AM, Baelde HJ, Monge M, Vos JB, de Boer HC, *et al*: Antagomir-mediated silencing of endothelial cell specific microRNA-126 impairs ischemia-induced angiogenesis. J Cell Mol Med 13 (8A): 1577-1585, 2009.
93. Panda H, Pelakh L, Chuang TD, Luo X, Bukulmez O and Chegini N: Endometrial miR-200c is altered during transformation into cancerous states and targets the expression of ZEBs, VEGFA, FLT1, IKKβ, KLF9, and FBLN5. Reprod Sci 19: 786-796, 2012.
94. Rekker K, Saare M, Roost AM, Kaart T, Sõritsa D, Karro H, Sõritsa A, Simón C, Salumets A and Peters M: Circulating miR-200-family micro-RNAs have altered plasma levels in patients with endometriosis and vary with blood collection time. Fertil Steril 104: 938-946.e2, 2015.
95. Misir S, Hepokur C, Oksasoglu B, Yildiz C, Yanik A and Aliyazicioglu Y: Circulating serum miR-200c and miR-34a-5p as diagnostic biomarkers for endometriosis. J Gynecol Obstet Hum Reprod 50: 102092, 2021.
96. Papari E, Noruzinia M, Kashani L and Foster WG: Identification of candidate microRNA markers of endometriosis with the use of next-generation sequencing and quantitative real-time polymerase chain reaction. Fertil Steril 113: 1232-1241, 2020.
97. Nisenblat V, Sharkey DJ, Wang Z, Evans SF, Healey M, Ohlsson Teague EMC, Print CG, Robertson SA and Hull ML: Plasma miRNAs display limited potential as diagnostic tools for endometriosis. J Clin Endocrinol Metab 104: 1999-2022, 2019.

98. Wang WT, Zhao YN, Han BW, Hong SJ and Chen YQ: Circulating microRNAs identified in a genome-wide serum microRNA expression analysis as noninvasive biomarkers for endometriosis. J Clin Endocrinol Metab 98: 281-289, 2013.
99. Zafari N, Tarafdari AM, Izadi P, Noruzinia M, Yekaninejad MS, Bahramy A and Mohebalian A: A Panel of Plasma miRNAs 199b-3p, 224-5p and Let-7d-3p as non-invasive diagnostic biomarkers for endometriosis. Reprod Sci 28: 991-999, 2021.
100. Marí-Alexandre J, Carcelén AP, Agababyan C, Moreno-Manuel A, García-Oms J, Calabuig-Fariñas S and Gilabert-Estellés J: Interplay Between MicroRNAs and oxidative stress in ovarian conditions with a focus on ovarian cancer and endometriosis. Int J Mol Sci 20: 5322, 2019.
101. Zhou S, Huang C, Wang W and Liu J: MiR-370-3p inhibits the development of human endometriosis by downregulating EDN1 expression in endometrial stromal cells. Cell Biol Int 45: 1183-1190, 2021.
102. Khan M, Shah PM, Khan IA, Islam SU, Ahmad Z, Khan F and Lee Y: IoMT-Enabled Computer-Aided Diagnosis of pulmonary embolism from computed tomography scans using deep learning. Sensors (Basel) 23: 1471, 2023.
103. Mohd Aman AH, Hassan WH, Sameen S, Attarbashi ZS, Alizadeh M and Latiff LA: IoMT amid COVID-19 pandemic: Application, architecture, technology, and security. J Netw Comput Appl 174: 102886, 2021.
104. Wang F, Wang H, Jin D and Zhang Y: Serum miR-17, IL-4, and IL-6 levels for diagnosis of endometriosis. Medicine (Baltimore) 97: e10853, 2018.
105. Menzhinskaya IV, Pavlovich SV, Melkumyan AG, Chuprynin VD, Yarotskaya EL and Sukhikh GT: Potential significance of serum autoantibodies to endometrial antigens, α-Enolase and hormones in non-invasive diagnosis and pathogenesis of endometriosis. Int J Mol Sci 24: 15578, 2023.
106. Mathiasen M, Egekvist AG, Kesmodel US, Knudsen UB and Seyer-Hansen M: Similar evolution of pain symptoms and quality of life in women with and without endometriosis undergoing assisted reproductive technology (ART). Acta Obstet Gynecol Scand 98: 77-85, 2019.
107. Gao Y, Liu P and Shi R: Anlotinib as a molecular targeted therapy for tumors. Oncol Lett 20: 1001-1014, 2020.
108. He Y, Hung SW, Liang B, Zhang R, Gao Y, Chu CY, Zhang T, Xu H, Chung JPW and Wang CC: Receptor tyrosine kinase inhibitor sunitinib as novel immunotherapy to inhibit myeloid-derived suppressor cells for treatment of endometriosis. Front Immunol 12: 641206, 2021.
109. Yildiz C, Kacan T, Akkar OB, Karakus S, Kacan SB, Ozer H and Cetin A: Effects of pazopanib, sunitinib, and sorafenib, Anti-VEGF agents, on the growth of experimental endometriosis in rats. Reprod Sci 22: 1445-1451, 2015.
110. Iampietro C, Brossa A, Canosa S, Tritta S, Croston GE, Reinheimer TM, Bonelli F, Carosso AR, Gennarelli G, Cosma S, *et al*: Quinagolide treatment reduces invasive and angiogenic properties of endometrial mesenchymal stromal cells. Int J Mol Sci 23: 1775, 2022.
111. Pellicer N, Galliano D, Herraiz S, Bagger YZ, Arce JC and Pellicer A: Use of dopamine agonists to target angiogenesis in women with endometriosis. Hum Reprod 36: 850-858, 2021.
112. Hamid AM, Madkour WA, Moawad A, Elzaher MA and Roberts MP: Does cabergoline help in decreasing endometrioma size compared to LHRH agonist? A prospective randomized study. Arch Gynecol Obstet 290: 677-682, 2014.
113. Mendoza-Torreblanca JG, Cárdenas-Rodríguez N, Carro-Rodríguez J, Contreras-García IJ, Garciadiego-Cázares D, Ortega-Cuellar D, Martínez-López V, Alfaro-Rodríguez A, Evia-Ramírez AN, Ignacio-Mejía I, *et al*: Antiangiogenic effect of dopamine and dopaminergic agonists as an adjuvant therapeutic option in the treatment of cancer, endometriosis, and osteoarthritis. Int J Mol Sci 24: 10199, 2023.
114. Olivares C, Ricci A, Bilotas M, Barañao RI and Meresman G: The inhibitory effect of celecoxib and rosiglitazone on experimental endometriosis. Fertil Steril 96: 428-433, 2011.
115. Zhang S, Zhuang L, Liu Q, Yu X, Min Q, Chen M and Chen Q: Rosiglitazone affects the progression of surgically-induced endometriosis in a rat model. Mol Med Rep 23: 35, 2021.
116. Nenicu A, Körbel C, Gu Y, Menger MD and Laschke MW: Combined blockade of angiotensin II type 1 receptor and activation of peroxisome proliferator-activated receptor-γ by telmisartan effectively inhibits vascularization and growth of murine endometriosis-like lesions. Hum Reprod 29: 1011-1024, 2014.
117. Nenicu A, Gu Y, Körbel C, Menger MD and Laschke MW: Combination therapy with telmisartan and parecoxib induces regression of endometriotic lesions. Br J Pharmacol 174: 2623-2635, 2017.
118. Nasu K, Nishida M, Ueda T, Yuge A, Takai N and Narahara H: Application of the nuclear factor-kappaB inhibitor BAY 11-7085 for the treatment of endometriosis: An in vitro study. Am J Physiol Endocrinol Metab 293: E16-E23, 2007.
119. Zhang JJ, Xu ZM, Chang H, Zhang CM, Dai HY, Ji XQ, Li C and Wang XF: Pyrrolidine dithiocarbamate attenuates nuclear factor-κB activation, cyclooxygenase-2 expression and prostaglandin E2 production in human endometriotic epithelial cells. Gynecol Obstet Invest 72: 163-168, 2011.
120. Huang R, Chen S, Zhao M, Li Z and Zhu L: Ginsenoside Rg3 attenuates endometriosis by inhibiting the viability of human ectopic endometrial stromal cells through the nuclear factor-kappaB signaling pathway. J Gynecol Obstet Hum Reprod 49: 101642, 2020.
121. Vallée A and Lecarpentier Y: Curcumin and Endometriosis. Int J Mol Sci 21: E2440, 2020.
122. Chowdhury I, Banerjee S, Driss A, Xu W, Mehrabi S, Nezhat C, Sidell N, Taylor RN and Thompson WE: Curcumin attenuates proangiogenic and proinflammatory factors in human eutopic endometrial stromal cells through the NF-κB signaling pathway. J Cell Physiol 234: 6298-6312, 2019.
123. Wei X and Shao X: Nobiletin alleviates endometriosis via down-regulating NF-κB activity in endometriosis mouse model. Biosci Rep 38: BSR20180470, 2018.
124. Uludag SZ, Demirtas E, Sahin Y and Aygen EM: Dienogest reduces endometrioma volume and endometriosis-related pain symptoms. J Obstet Gynaecol 41: 1246-1251, 2021.
125. Keleş CD, Vural B, Filiz S, Vural F, Gacar G, Eraldemir FC and Kurnaz S: The effects of etanercept and cabergoline on endometriotic implants, uterus and ovaries in rat endometriosis model. J Reprod Immunol 146: 103340, 2021.
126. Ren XU, Wang Y, Xu G and Dai L: Effect of rapamycin on endometriosis in mice. Exp Ther Med 12: 101-106, 2016.
127. Grammatis AL, Georgiou EX and Becker CM: Pentoxifylline for the treatment of endometriosis-associated pain and infertility. Cochrane Database Syst Rev 8: CD007677, 2021.
128. Dicitore A, Castiglioni S, Saronni D, Gentilini D, Borghi MO, Stabile S, Vignali M, Di Blasio AM, Persani L and Vitale G: Effects of human recombinant type I IFNs (IFN-α2b and IFN-β1a) on growth and migration of primary endometrial stromal cells from women with deeply infiltrating endometriosis: A preliminary study. Eur J Obstet Gynecol Reprod Biol 230: 192-198, 2018.
129. Söderman L, Böttiger Y, Edlund M, Järnbert-Pettersson H and Marions L: Adjuvant use of melatonin for pain management in endometriosis-associated pelvic pain-A randomized double-blinded, placebo-controlled trial. PLoS One 18: e0286182, 2023.
130. Vašková J, Klepcová Z, Špaková I, Urdzík P, Štofilová J, Bertková I, Kľoc M and Rabajdová M: The importance of natural antioxidants in female reproduction. Antioxidants (Basel) 12: 907, 2023.
131. Schwertner A, Conceição Dos Santos CC, Costa GD, Deitos A, de Souza A, de Souza IC, Torres IL, da Cunha Filho JS and Caumo W: Efficacy of melatonin in the treatment of endometriosis: A phase II, randomized, double-blind, placebo-controlled trial. Pain 154: 874-881, 2013.
132. Santanam N, Kavtaradze N, Murphy A, Dominguez C and Parthasarathy S: Antioxidant supplementation reduces endometriosis-related pelvic pain in humans. Transl Res 161: 189-195, 2013.
133. Li Y, Zeng X, Lu D, Yin M, Shan M and Gao Y: Erastin induces ferroptosis via ferroportin-mediated iron accumulation in endometriosis. Hum Reprod 36: 951-964, 2021.
134. Bouquet de Joliniere J, Fruscalzo A, Khomsi F, Stochino Loi E, Cherbanyk F, Ayoubi JM and Feki A: Antiangiogenic therapy as a new strategy in the treatment of endometriosis? The first case report. Front Surg 8: 791686, 2021.
135. Bodnar RJ: Anti-Angiogenic Drugs: Involvement in cutaneous side effects and wound-healing complication. Adv Wound Care (New Rochelle) 3: 635-646, 2014.