



AN INSIGHT INTO ENDOMETRIOSIS: ROLE AND INFLUENCE OF THE PROCESS OF ANGIOGENESIS

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ABSTRACT

Introduction: Endometriosis is one of the most common gynaecological disorders present in females. According to the implantation of ectopic endometrial tissue outside of the uterine cavity, angiogenesis is an essential prerequisite for the progression of the disease.

The purpose is to provide insight and a better understanding of the role that angiogenetic factors play within endometriosis and how this can translate into more effective diagnostic and therapeutic approaches taken by medical specialists when treating this disease.

Materials and methods: We conducted a review of the available scientific literature on PubMed, Google Scholar and Science Direct, which included randomized controlled trials, observational studies, prospective controlled studies and case reports.

Results and Discussion: Our review of the scientific literature showed that the role of angiogenesis upon the development of endometrial ectopic tissue is very significant, and a positive relationship is established with an increase in neo-angiogenesis and a quicker rate of development of ectopic endometrial tissue. We also found data indicating that there are a multitude of angiogenetic and anti-angiogenetic factors functioning in a homeostatic manner to provide an optimal environment for the endometrial tissue to proliferate and for translocation for the implantation of the ectopic tissue within different locations both within the uterine cavity and distant anatomical locations and regions located outside of the uterine cavity.

Conclusion: Recently, the research surrounding the process of angiogenesis is positive and positive correlations have been established between the role of angiogenesis and the extent to which the ectopic endometrial tissue proliferates.

Keywords: endometriosis, infertility, polymorphism, incidence, morphogenesis,

INTRODUCTION

Endometriosis is an oestrogen-dependent inflammatory disease that is characterized by the presence of endometrial glands and stroma outside the realms of the uterus. It can lead to chronic inflammatory reactions that may result in the formation of scar tissue, such as adhesions and/or fibrosis, confined within the pelvis. [1] Clinically, there are types characterized by way of lesion type, and these include; Superficial endometriosis, which is found mainly in the pelvic peritoneum; cystic ovarian endometriosis, which is found in the ovaries, deep endometriosis, which is found in the recto-vaginal septum, bladder, bowel and in some rare cases it can also be found outside of the pelvis. Endometriosis lesions are primarily located on the pelvic peritoneum and ovaries but can slowly disseminate via hematogenic and lymphatic routes to the pericardium, pleura of the lung, lung parenchyma and in some cases, it can manifest within the meninges of the brain. The aetiological factors influencing the onset of endometriosis are retrograde menstruation, coelemic metaplasia, haematogenic and lymphatic spread, remnants of the Mullerian ducts and various interleukins and growth factors produced within the endometrial stromal or progenitor cells. The prevalence of the disease is varied due to the heterogeneous clinical manifestations, which include dysmenorrhea, dyspareunia, dysuria and chronic or severe long-lasting abdominal pain, and in some cases infertility leading to a severe limitation in the quality of life. [2, 3] The development of endometriosis is proposed as retrograde menstruation, which is, in fact, where the menstrual blood and uterine tissues enter the peritoneal cavity by way of the fallopian tubes. [4] However, in more than 90% of women participating in investigations such as laparoscopy, it has been revealed that, in fact, the theory of retrograde menstruation facilitated the transport of endometrial tissue to the peritoneal cavity; however, an external factor is responsible for increasing the susceptibility of certain women to experience this implantation and growth of this ectopic endometrium. [5] Within this, other theories have been suggested, such as an altered peritoneal environment, immunological susceptibility and a greater amount of retrograde menstruation and not to mention the influence of genetic predisposition, which can increase the likelihood of this atypical process of endometriosis to occur. In addition

to this, it can be proposed that the undergoing of proliferation, secretion, regression and regeneration of the endometrial lining of the uterus during the period of the menstrual cycle can influence the pathological atypicality of the endometrium in subtle alterations in the events that take place during the menstrual phase. One of the main theories includes the ability of the endometrium to divide and, hence, the resulting implantation and growth within the peritoneal cavity. Furthermore, within the complex series of events that arise within the menstrual cycle, the role of blood vessel proliferation and stimulation of endometrial gland development is important, and three different separate episodes of angiogenesis of blood vessels have been proposed and comprise of post-menstrual repair during the early proliferative phase, mid-proliferative phase growth under the direct influence of oestrogen and growth of the coiling of the spiral arteries and arterioles situated in the stratum functionalis of the endometrium which is influenced by the presence and production of progesterone via the corpus luteum in the secretory or luteal phase of the menstrual cycle. [6] The presence of angiogenesis within the endometrium can be denoted via laparoscopy, and findings include dense vascularization. In early lesions, blood vessels appear pink-red with a high blood vessel density, dilated vascular structures and an increased number of immature vessels when compared with black lesions and a general increase in vascularization surrounding the area of abnormal vessel geography. Researchers and specialists within this field have been investigating the angiogenetic processes within the endometrium in order to develop anti-angiogenetic treatment strategies, which may reduce the side effects and recurrences seen in women undergoing conventional conservative therapies or mainstream surgical treatment. This review article will look at the angiogenetic factors and pathophysiological processes that occur within the endometrium and whether this information is sufficient in the diagnosis and treatment of endometriosis. [7, 8]

MATERIALS AND METHODS

We conducted a review of the available scientific literature at Pub Med, Google, Science Direct, which included randomized trials, prospective controlled trials, research reports and guidelines in the approach taken in the research of angiogenetic factors influencing endometriosis in terms of development and clinical application of treatment strategies involving angiogenetic factors. In the Scientific literature, we searched for outcomes that included Endometriosis, Pathophysiology of Endometriosis, therapy of endometriosis, angiogenetic factors, angiogenetic theories proposed in the process of endometriosis. We have also included research and analysis of conventional treatment methods utilized in the treatment of endometriosis that may have an impact on the development of angiogenetic factor treatment therapies, which can be used in treating endometriosis.

DISCUSSION

Our review of the scientific literature indicated evidence of the importance of angiogenetic processes within the pathophysiological development of endometriosis and whether new mainstream forms of treatment can be developed based on the proposed theories to revolutionize the way obstetricians and gynaecologists treat women suffering from this disease.

Obstetrics and gynaecology is a medical speciality which is widely needed as it is a dual-speciality both working to keep pregnancies healthy whilst being responsible for the delivery of viable foetuses, and it also focuses on the broader spectrum of issues relevant to a woman, specifically the health and disease manifestation of the female reproductive system. A normal endometrial lining of the uterus, the proposed mechanism of angiogenesis occurs in the form of vessel elongation rather than a branch spouting of the spiral arteries, and it is the primary mechanism for development and growth of the endometrium during the first 14 days of the menstrual cycle namely known as the proliferative phase. However, it seems that there is a recruitment of new capillaries from existing adjacent peritoneal microvessels in conjunction with this, it is also essential to mention the importance of the newly synthesized blood vessels derived from the circulation endothelial progenitor cells in a process called vasculogenesis, which is also involved in the pathogenesis of endometriosis. The endometrium is a dynamic tissue which displays various properties, such as populations of clonogenic epithelial and stromal stem cells that require indefinitely active cyclical angiogenesis. [9, 10]

Endometriosis can produce various chemotactic factors, such as cytokines and growth factors, that regulate their proliferation and vascularization. Interleukin-1 Beta is an important interleukin-1 secreted by the peritoneal macrophages, and it plays a pivotal part in the neovascularization of the endometriotic like lesions. In addition to this, IL-6 is a multi-subunit and multifunctional protein which promotes endometrial cellular proliferation and angiogenesis, and its production is elevated in endometriosis and the concentrations of IL-6 can be found in high quantities in the peritoneal fluid of such individuals. IL-8 is worth mentioning as it is a pro-inflammatory cytokine that induces the chemotaxis of neutrophils and has a potent stimulatory effect on the angiogenetic mechanism. The presence of IL-1B influences and increases the angiogenetic factors in neutrophils to stimulate endometriosis-associated angiogenesis. On the other hand, in the presence of specific transcription factors, hypoxic-inducible factors enhance the expression of pro-angiogenetic factors like VEGF to induce hypoxia-induced angiogenesis. In the presence of transcriptional factor HIF-1 alpha, VEGF m-rna expression levels increase in response to hypoxia; moreover, the HIF-1 alpha factor is responsible for regulating the expression of transcriptional genes encoded in the transcriptional synthesis of VEGF to induce hypoxemic-induced angiogenesis. [11]

Activin A is a growth factor member of TGF-beta with subsequent effects on inflammation and angiogenesis. The human endometrium is both a source and target of Activin A, and it can both up and down-regulate the expression and secretion of IL-8 and vascular endothelial growth factor, which are produced from the endothelial stromal cells. Consequently, the vascular growth factor is the most potent and specific angiogenetic factor responsible for a variety of effects such as endothelial cell proliferation and migration, organization of endothelial cells into tubular like structures, and increase in permeability, all of which participate in the endometrial angiogenetic cascade. The basis of the so-called vascular endothelial growth factor is influenced by the presence and levels of oestrogen, which in the late proliferative phase of the menstrual cycle increases in quantity VEGF to promote the proliferation and neovascularization of the endometrium in order to prepare the endometrial lining of the uterus for conception and implantation of the blastocyst which is being brought in via the fallopian tubes from the ovaries, however, it is important to note that the concentration of VEGF is at its peak in the secretory phase and phase of menses.

Angiogenesis can occur throughout fetal growth and development, but in adults, it is concentrated in the menstrual cycle, the ovaries in the liberation of the mature graafian follicle and formation of corpus luteum and in various pathological conditions such as wound healing, diabetic retinopathy, tumour growth and not to mention endometriosis. Specifically within the menstrual cycle, the process of angiogenesis plays a crucial role in the follicular maturation development of a functional corpus luteum. The importance of angiogenesis within endometriosis is such that the nova vasculogenesis that takes place from pre-existing blood vessels is necessary for the survival and progression of ectopic endometrial tissue situated outside of the uterine cavity. Oestrogen is an important hormone within the menstrual cycle and plays an important role in the development of blood vessels for endometriotic implants. The 17-Beta estradiol up-regulates the VEGF expression in the endometrial human stromal cells by activating the Wnt/B-catenin axis through estrogenic receptors and thus enhances their ability to establish a new blood supply to the endometrium. Furthermore, estrogenic receptors of the beta sub-type directly regulate the expression of genes involved in hypoxia-induced angiogenesis, such as HIF-1 alpha, VEGF, angiotensin 1 receptors in ectopic lesions of the endometrium to support the progression of endometriosis. In addition to this, there are various other factors which interact with one another to up-regulate or inhibit the activation of VEGF within the endometrial tissue. For example, peptide hormones regulate angiogenesis by stimulation or inhibition to promote or prevent the growth of the ectopic tissue and through the process of proteolysis, we have a conversion of the original hormone into either a pro-angiogenetic peptide, which is a stimulating factor in the progression of ectopic endometrial tissue, or it can lead to anti-angiogenic peptide formation which acts in an inhibitory form preventing the progression of ectopic endometrial tissue.

Furthermore, if we look at the findings, it demonstrates that angiogenesis within endometriosis is influenced by an interaction of various intra and extracellular signalling molecules, which interact with one another and are influenced by local hypoxic and inflammatory stimuli within the specific microenvironment of the peritoneal cavity. The ability to determine the type of transcriptional factors and hormonal elements and the extent of influence of endometriosis is very difficult because different endometrial phenotypes markedly have different levels of genetic expression levels of genes associated with hypoxia and angiogenesis. With regards to endometriosis and the influence of angiogenesis on a clinical basis, we can say that within the role of angiogenesis and influence over the progression of endometriosis is reflected in the fact that the peritoneal fluid from endometriosis patients significantly increases the proliferation of endothelial cells and induces a strong vascular reaction leading to new blood vessel formation within the ectopic tissue of endometrium type. This is due to the fact that peritoneal fluid contains elevated concentrations of different angiogenetic promoting factors such as VEGF, insulin growth factor 1, angiotensin-2, erythropoietin, hepatocyte growth factor and on the other hand the peritoneal fluid also contains lower concentrations of anti-angiogenetic factors namely adiponectin, interferon-gamma induced protein-10. These findings are interesting as they serve as a basis that when diagnosing endometriosis, we may be able to use the interaction of these pro and anti-angiogenetic factors as biomarkers for determining a working diagnosis of endometriosis as well as for assessing the efficacy of therapeutic approaches taken to treat endometriosis. However, although promising studies have indicated a positive indication of these factors as biomarkers in endometriosis, as of yet, they are of insufficient diagnostic sensitivity and specificity. This can be explained by the low study sample or the heterogeneous diseases stages of the subjects within the study sample. To further this, it is important to use a combination of biomarkers to diagnosis endometriosis. Currently, such proposals for utilizing these tools can only be used to assess the risk of developing endometriosis or adenomyosis. [12, 13] In line with the proposal to use medicinal compounds containing anti-angiogenetic constituents, it has shown to be a promising target for gene therapy or pharmacological-based treatment of endometriosis. These include growth factor inhibitors, endogenous angiogenesis inhibitors, fumagillin analogues and statins, immunomodulators in which these medicaments have been proven to reduce the micro vessel density of endometriotic lesions in animal models with a resulting effect of engrafted lesions or a suppressed lesion growth. In studies carried out on mice, the concept of treatment containing angiogenetic compounds, the blood vessels invading the endometrium are accompanied by nerve fibres. These nerve fibres stimulate the dorsal root neurons within the central nervous system, which increases the pain perception in endometriosis patients. Due to this finding, the treatment of endometriosis with anti-angiogenetic compounds not only leads to a reduction of blood vessel formation but also nerve fibre growth in the ectopic tissue.

Despite the promising results, anti-angiogenic therapy has not been implemented for clinical use because of several reasons. The first is because endometriosis is a heterogeneous disease with diverse types of lesions in different locations, and so each location containing ectopic endometrial tissue will have a varying degree of vascularization and composition. Anti-angiogenic compounds target the early red lesions with a high level of angiogenic activity and immature micro vessels, so the older, black and white lesions may be resistant to this form of treatment. Thus, the administration of anti-angiogenic compounds may not be suitable as a monotherapeutic drug focusing on pharmacological-based eradication as well as eradication of well-established endometriotic lesions in the peritoneal cavity. However, the anti-angiogenic compounds may serve as an importance in the prevention of new lesion formation after surgical removal and, therefore, can help to reduce high recurrence rates of surgical based endometriosis therapies. In addition to this, the resistance to anti-angiogenic drugs poses an issue with the usage of anti-angiogenic compounds, but this can be overcome by simultaneously suppressing different angiogenic compounds or by means of combination therapy. Finally, the women who suffer from endometriosis are of reproductive age and may wish to preserve their fertility; this poses as a problem as the fertility and uterus are heavily dependent upon the physiological angiogenesis in the ovary, uterus and placenta and, therefore, the long-term administration of anti-angiogenic agents is contraindicated due to the unknown effects on the female reproductive organs which may compromise the ability of the women to conceive and bear a child should the female have the desire or wish to have children. In order to overcome this, trials are currently being carried out utilizing anti-angiogenic agents with a more acceptable and safe profile to see whether the same adverse effects are produced or if milder side effects are present, which can be contained with combined therapy. [14]

Anti-angiogenic agents are agents which block the action of VEGF and inhibit the ability of VEGF to initiate arteriole proliferation and neogenesis. Bevacizumab is a recombinant human monoclonal antibody that inhibits VEGF, inhibiting the development and proliferation of endometriotic lesions with a reduction in the vascular density and increased apoptosis with a reduction of VEGF levels in the peritoneal fluid. Sorafenib is another anti-angiogenic agent, which in its form is an orally active

multikinase inhibitor that interferes with the activity of the VEGF receptor and tyrosine kinase receptors, and in the mice model, it reduces the micro vessel density and lesion volume in patients suffering from endometriosis. Lipoxin A4 is an endogenous eicosanoid whose role is to regulate inflammation. This lipid-based medicament blocks the migration of endothelial cells and VEGF-stimulated angiogenesis. The Lipoxin A4 reduces the endometrial lesion size and down regulates the inflammation-associated proteins such as IL-6, VEGF and matrix metalloproteinase 9. Parecoxib, a selective cyclooxygenase-2 inhibitor, reduces the lesion size, micro vessel density, the number of macrophages and the expression of VEGF, which leads to atrophy and regression of endometrial ectopic tissues when carried out on mice. Statins are inhibitors of HmG-COA with an intrinsic antioxidant, anti-inflammatory and anti-angiogenic properties, for example, Atorvastatin inhibited the inflammatory and angiogenetic genes COX-2 and VEGF in endometrial stromal cells. Another important anti-angiogenic agent is the dopamine agonist cabergoline, which exerts its effect through VEGFR-2 inactivation, inhibiting the growth of established endometrial lesions. Finally, progestogens reduce the proliferation of endometrial stromal cells and suppress the transcription of VEGF-A and the microvessel density in human ectopic endometrial lesions. [15, 16]

CONCLUSION

Within the last decade, it has become evident that the process of angiogenesis plays a central role in the pathogenesis of endometriosis. Many angiogenetic inducing factors can be determined, such as VEGF, which is present in peritoneal fluid and ectopic endometrial tissue from endometriotic patients. However, despite all of this, there is still limited evidence in the knowledge of understanding the mechanisms behind blood vessel angiogenesis and the complex and dynamic interactions between various factors and pathophysiological processes which work together to regulate angiogenesis specifically within the endometrium. To conclude, more research is needed on the mechanisms of angiogenesis and the general physiological process of developing new blood vessels within the endometrial ectopic tissue to ascertain a broader and more complete understanding of endometriosis.

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