Innovative approach in assessing the role of neurogenesis, angiogenesis, and lymphangiogenesis in the pathogenesis of external genital endometriosis

T. Sheveleva¹, V. Bejenar², E. Komlichenko², A. Dedul²,³, and A. Malushko⁴

¹Department of Gynecology, ²Department of Obstetrics – Gynecology and Neonatology, Clinic of Obstetrics and Gynecology, St. Petersburg State Medical University Named After Academician I. P. Pavlov, Saint Petersburg, Russia, ³Department of Family Planning and Human Reproduction, University Hospital of Saint-Petersburg State University, Saint-Petersburg, Russia, and ⁴Department of Gynecology, University Hospital of Saint-Petersburg State University, Saint-Petersburg, Russia

Abstract
Endometriosis is a chronic, progressive, relapsing estrogen-dependent disorder characterized by the growth of tissue structure and function similar to the endometrium outside the normal mucosa of the uterine cavity localization. Endometriosis is found in 10–15% of women in reproductive age and it is one of the main causes of pelvic pain syndrome and infertility. Mechanisms of the development of endometriosis and related pathological pain impulses are still poorly understood and therapeutic approaches do not always have a sufficient effect; in this connection, the study of the pathogenesis of endometriosis and endometriosis-associated pain currently is perspective. Identification of significant factors of angiogenesis, lymphangiogenesis, and neurogenesis in the external genital endometriosis will promote the development of non-invasive early diagnosis and pathogenetic therapy.

Keywords
Angiogenesis, endometriosis, innovation, lymphangiogenesis, neurogenesis, pelvic pain

Introduction
Endometriosis is a chronic disease manifested by the presence of foci of tissue, similar to the endometrium of the uterus outside its cavity. Endometriosis remains the subject of controversy: discussions are under way about its etiology, pathogenesis, and treatment. It can cause chronic pelvic pain, dyspareunia, diskhezii, and infertility in women.

Now there is no one doubt that links between infertility and endometriosis.

According to the current literature, from 25% to 50% of women with endometriosis have infertility, and 30–50% of women with endometriosis are infertile [1]. According to Guo [2], the incidence of endometriosis in women with chronic pelvic pain syndrome is more than 33%. Meuleman et al. in 2009 evaluated the occurrence of endometriosis in infertile women with ovulatory cycles and a healthy partner. The frequency of endometriosis in this category of women was 47%, while in 63% of the cases detected I and II stages of the pathology as classified by the American Fertility Society 1996 [1].

One of the most common clinical symptoms of endometriosis is pelvic pain. The mechanisms associated with endometriosis pain are complex as the pathogenesis of the disease. It is well known that there is no clear correlation between the degrees of prevalence of endometriosis is observed, such as laparoscopy and the severity of pain symptoms [3]. However, the degree of the localization of rectovaginal endometriosis pain intensity is associated with the depth of the spread of endometriosis [4].

On one hand, observations suggest that endometriosis is found in the one-third of the cases of women undergone laparoscopy for chronic pelvic pain [5]. On the other hand, according to some investigators, asymptomatic endometriosis was found in 14% of women who have undergone surgical sterilization [6].

A serious problem of endometriosis is fairly early start of menstrual pain (an average age of patients with endometriosis is 25–30 years) and a significant time delay (7–11 years) between the detection of the disease and the diagnosis [6]. About 70% of adults who complained of dysmenorrhea were eventually diagnosed endometriosis, which can be the basis for a more careful examination of young patients with corresponding symptoms [7]. On an average, women consulted seven specialists before being diagnosed and begin treatment [6].

Making a true estimate of the incidence of endometrial disease is difficult, as the only reliable way to diagnose is currently endometriosis visualization during diagnostic laparoscopy and subsequent histological confirmation of the diagnosis.

Thus, endometriosis is a disease that affects the majority of women of reproductive age, negatively affecting their physical, psychological, and social condition that significantly reduces the quality of life in this category of patients [1,2].

Despite extensive research, mechanisms for the development of endometriosis and related pathological pain impulses are still
poorly understood, and there are several theories about the origin of endometriosis.

The most well-explained theory seems to be first proposed in 1921 by Sampson, the theory of retrograde implantation of endometrial fragments of menstrual blood thrown into the abdominal cavity and its growth, with the formation of endometrioid heterotopias and their dissemination in the lymphatic and circulatory vasculature.

The processes of angiogenesis, lymphangiogenesis, and neurogenesis, providing formation and growth of blood and lymphatic vessels and nerve fibers, underlie the pathogenetic mechanisms of development of endometriotic lesions [8].

Neurogenesis, angiogenesis, and lymphangiogenesis are crucial process in the endometrium and in particular, endometriosis, because of their role in the healing of injuries, growth, and spread of tumors and the generation of pain. The mother angiogenesis, lymphangiogenesis, and neurons are vital to repair, regeneration, growth, and differentiation of the endometrium which are controlled by estrogen and progesterone. In contrast to angiogenesis and lymphangiogenesis, little is known about the mother of endometrial neurogenesis; however, it is extremely important in the generation of the value of endometriosis-associated pain [9].

Development of pain includes a number of mechanisms and the interactions between the peripheral and the central nervous system [9]. Studies indicate the existence of a direct innervation of endometrioid heterotopias [10], as well as for changes in the peripheral and the central nervous system in women with endometriosis-associated pain [11].

**Angiogenesis**

The processes of angiogenesis are the most important mechanisms involved in the growth and remodeling of the endometrium. Endometrium is defined as vessels exposed to cyclic endometrial growth and regression during the menstrual cycle, under the influence of estrogen and progesterone [9]. Angiogenesis is regulated by a large number of different molecules: promoters and inhibitors [12].

Endometrioid heterotopias synthesized a number of factors that stimulate angiogenesis. Among these factors, the most important are VEGF-A and its receptor (VEGFR-2), angiopoietins -1 and -2. According to some studies, the expression of VEGF-A and its receptor in endometriotic lesions is significantly higher compared with the endometrium [13], according to other studies – with intact peritoneum [14].

According to the authors, different types of endometrioid heterotopias may exhibit varying degrees of expression of proangiogenic factors. For example, red endometriotic lesions are more pronounced processes of vascularization and cell proliferative activity [15]. Data on the increase of the concentration of soluble VEGF-A in peritoneal fluid in women with endometriosis are available in the literature [13,16].

According to Lee et al. [17], the expression of proangiogenic factor prokinetitsina-1 (PK-1) is significantly increased in endometriotic lesions compared with the endometrium and also observed decreased expression of factors that inhibit angiogenesis, such as thrombospondin-1 (TSP-1) [13–15].

In the presence of estradiol, a potent angiogenic factor, activated immune and neuroendocrine cells also promote angiogenesis, which is secreted by a variety of pro-angiogenic and pro-inflammatory cytokines (II-1, II-6, and II-8), tumor necrosis factor – alpha (TNF-a) [18], endometrial cells secrete matrix metalloproteinases-1 and -2. Adhesion occurs by the activation of cell adhesion molecule sICAM-1, oxidative stress, and inflammatory processes which are supported by activated immune cells [19].

**Lymphangiogenesis**

Relatively little is known about lymphangiogenesis, but a number of studies have noted an increase in the expression of endometriotic lesion factors stimulating lymphangiogenesis, such as VEGF-C and D [14], and in a significant degree in the deep infiltrating endometriosis lesions compared with heterotopias, localized in the peritoneum and ovaries [20]. It was found to increase in endometriotic lesions [21,22], peritoneal fluid [23], and other growth factors such as IGF-1 and IGF-2 in patients with deep infiltrating endometriosis, at the same time a correlation between their concentration and proliferative activity of endometrial heterotopias was observed [24]. A significant increase in the density of lymphatic vessels in the stroma of endometrial lesions was found.

**Neurogenesis**

According to studies, the processes are involved in the neurogenesis growth and the development of endometriotic lesions. Violations of the local inflammatory response, hormonal and local angiogenesis contribute to the growth of nerve fibers. The presence of nerve fibers in the functional area of endometrial lesions plays a key role in the formation and perception of pain impulses; however, the precise mechanisms of endometriosis-associated pain are still unclear.

The nervous tissue in the endometriotic lesions presented sensitive, adrenergic, and cholinergic fibers. These fibers are involved in carrying the pain which may be associated with the formation of pain associated with endometriosis. An increase in the density of nerve fibers of the pelvic peritoneum causes hyperinnervation. These nerve fibers become a potential abnormally increased functionality. Thus, not only increasing the number of nerve fibers but also processes for their excitation can be broken as a result of abnormal neurogenesis [25].

Studies were performed in animal models reflecting the mutual cross-influencing each other endometrial foci and eutopic endometrium of endometriosis [26]. Neurotrophins and their receptors and other molecules expressed neuronal activity in endometriotic lesions. Neurotrophins – family of regulatory proteins of the nervous tissue – are synthesized by neurons and surrounding cells, and promote the proliferation, differentiation, and maintenance of viability and function of the peripheral and central neurons. Neurotrophins act locally at the point of release and especially intensively induces branching of the dendrites (arborisation) and neurite outgrowth (sprouting) towards target cells.

To date results indicate the important role of neurogenesis in the processing of a number of molecules, including nerve growth factor (NGF), neurotrophins 3, -4/5, growth factor isolated from the brain (BDNF), neurotrophins 1B cell stimulation factor-3 (NNT-1/BSF-3), and glial cell neurotrophic factors (GDNF). NGF, neurotrophin-3, and their receptors TrkA and p75 are detected in the endometrial glands and stroma of peritoneal and ovarian endometriosis lesions and with deep infiltrative endometriosis [25]. According to various authors, ovarian endometriosis detects the expression of BDNF, NT-3, NT-4/5, slit ligand, and Robo receptors [25].

**Endometriosis-associated pain**

The formation of pain impulses in the development of endometriosis is caused by an inflammatory response involving macrophages, increased secretion of estrogen, cytokines, growth and remodeling tissue factors, and neurotrophins that stimulate the growth and activation of sensitive, sympathetic, and parasympathetic nerve fibers in the centers and the formation of persistent pain [27].
Changes in the endometrium of endometriosis

There is growing evidence that the endometrium in women with endometriosis is fundamentally different from the endometrium of healthy women, although routine histological study did not show significant differences. The combination of reducing apoptosis [28], depression immune surveillance [29], as well as the ability to increase the adhesion of the proteolytic activity [30], angiogenic potential proliferation [31], and estrogen production [32] in violation of the innervation determines the ability of this tissue to enhance the implantation and growth on the surface of the peritoneum and, ultimately, the formation, and the occurrence of endometriosis with corresponding symptoms.

Angiogenesis in the endometrium

A study comparing the endometrium of healthy women and women affected by endometriosis showed significant differences in the process of angiogenesis, manifested in an increase of expression of proangiogenic growth factors including vascular endothelial growth factor-A (VEGF-A)-angiopoietins -1 and -2 as well as receptors for these molecules [13–15,24]. Thus, there was a reduction in the expression of factors that inhibit angiogenesis, such as thrombospondin and prokinetins [33].

These data suggest a higher angiogenic potential of endometrial tissue of women with endometriosis and expected to increase the ability to ectopic endometrial invasion and survival in the abdominal cavity [34].

Lymphangiogenesis in the endometrium

There exists a considerable overlap between the mechanisms that control angiogenesis and lymphangiogenesis, involving molecules promoters and inhibitors, such as angiopoietins, integrins, fibroblast growth factor, hepatocyte growth factor, vascular growth factors C and D (VEGF-C, VEGF-D), insulin-like growth factors [35].

Relatively little is studied about the natural inhibitors of lymphangiogenesis. It is proved that the inhibitory effect was exerted on him by vazogibin-1, interferon-alpha, beta transforming growth factor, semaphorin 3F, and neostatin. In addition to the increase of the angiogenesis activity, there is an evidence of changes in the local lymphangiogenesis in women with endometriosis: reduced expression of vascular growth factor C; increased expression of vascular growth factor receptor 2, semaphorin E, and matrix metalloproteinase 7 [36]. There are observations which describe the spread of ectopic endometrial tissue in the lymph vessels and lymph nodes outside the endometrial cavity of the uterus [37].

Neurogenesis in the endometrium

According to various authors, in women with endometriosis expression of neurotrophins and their receptors and other neuronal active in eutopic endometrium of the uterus was increased as compared with healthy women. Thus, the expression of NGF and its receptor TrkA and p75 [38], as well as the expression BNDF and NT-4 were significantly increased [39].

Other irregularities in the eutopic endometrium of endometriosis associated with neurogenesis included increase of neurotransmitter number and immune cells producing neurotrophins including T cells, B cells, macrophages, NK-cells, dendritic cells, mast cells [40].

In addition to the detection of increasing of the neurogenesis promoters, expression in eutopic endometrium of women with endometriosis were found in the functional layer small unmyleinated nerve fibers (sensory C fibers) that are not detected in healthy endometrium [25].

Treatment

Treatment for endometriosis has three main objectives:
(a) the decrease in the intensity of pain;
(b) preventing recurrence of the disease;
(c) increase of the likelihood of pregnancy [24,40].

The treatment of endometriosis must use individual approach – the development of an optimum diagnostic and therapeutic individual program [40]. The goal of the treatment should be determined by the patient’s main problems (elimination of pain symptoms and/or bleeding, restore fertility, or just to improve the quality of life).

The first stage to diagnose and eliminate the anatomical substrate of endometriosis is often carried out with medical-diagnostic laparoscopy, which is the “gold” standard [41]. However, during the surgery, only visible endometriosis was removed and, in future, patients continue to suffer from pelvic pain. Laparoscopy should be performed only by a physician, who can, if necessary, carry out an adequate surgical treatment in full [42].

Prevention of relapse (for surgery)

According to the recommendations of the American Association of Reproductive Medicine (ASRM), endometriosis should be treated as a chronic disease that requires a long-term development plan for conducting patient with the maximum use of drug therapy in order to avoid repeated surgical interventions [43].

Most international recommendations for a first-line drug therapy for a long time attributed combine oral contraceptives (COCs) and progestins. Only in the case of unsuccessful outcome, their application is for 3 months. Recommended a second-line therapy including agonist of gonadotropin-releasing hormone (GnRHa) to ‘‘return’’ (‘‘add-back’’) treatment/therapy cover or left norgestrel-releasing system (Mirena), although not having formally registered indications for the treatment of endometriosis [41]. Treatment by other means, or a palliative (analogesics, anti-inflammatory drugs – NSAIDs), causes a large number of side effects (danazol and gestrinone) or experimental (aromatase inhibitors, selective estrogen receptor modulators, SERMs), agonists of estrogen receptor-b (ER b), antiangiogenic agents, etc.) [42].

The hormonal treatment of endometriosis should be guided by the basic principle that no drug can eliminate the morphological substrate of endometriosis, but only has an indirect effect on it, which explains the symptomatic and clinical benefit [42].

COCs are widely used to treat the symptoms of endometriosis, but judging according to research, the effect is negligible. A meta-analysis suggests that even though COCs suppress ovulation, which reduces the risk of endometriosis, estrogen component in their structure may actually stimulate the development of the disease [44].

Danazol is an androgenic steroid, which is sufficiently effective in the treatment of endometriosis. According to studies, more than 80% of the patients noted the disappearance of pain symptoms or significant pain relief [45], but its use is limited by side effects.

GnRH agonists are considered the gold standard for the treatment of endometriosis because of their high efficiency for the relief of pain, but their use is accompanied by estrogen-deficiency symptoms: hot flashes, vaginal dryness, decreased libido. Unfortunately, their hopes for the agonist of gonadotropin-releasing hormone and antigonadotropin fully justified [45].

A special attention is focused on medication dienogest, which is recommended as monotherapy for endometriosis in Europe, Japan, and others. It is a synthetic progestin oral progestogen with severe and moderate antigonadotropynm effects, but without androgen, glucocorticoid, and mineralocorticoid activity. The
experiments on animals also showed that dienogest induces apoptosis of ovarian granulosa cells [46].

The use of aromatase inhibitors is a new promising method for the treatment of endometriosis. These drugs reduce the local synthesis of estrogen in the endometrial heterotopias and also inhibit the formation of estrogen in the ovaries, brain, and adipose tissue [47]. The systematic review of these studies has shown that aromatase inhibitors significantly pronounced a decrease in pain as compared with GnRH agonists [48]. It is important to know that aromatase inhibitors cause significant loss of bone density with prolonged use and cannot be appointed as a monotherapy in premenopausal women.

Currently, a large number of studies in animal models are aimed at understanding the mechanisms that suppress pathological angiogenesis, and neurogenesis limfangio-, as well as the development of drugs is aimed at key pathogenetic links of endometriosis. Drugs are divided into groups of exclusive preparations, the only known function is to inhibit angiogenesis, and inclusive preparations of angiogenic activity which is related to other functions. The first group includes funds from direct (endogenous and synthetic angiogenesis inhibitors: endostatin, Short synthetic endostatin peptides, Capeolstatin, Lodamin) and indirect sources (Pro-angiogenic signaling blockers: Anti-VEGF-A antibodies, Soluble truncated VEGF-R1, VEGF-targeted gene therapy, Bevacizumab, 2-Methoxyestradiol, SU5416, SU6668, Sorafenib). The second group can be formed based on hormones and functionally related substances: progesterone, dydrogesterone, dihydrodydrogesterone, dienogest, danazol, leuprolide acetate; dopamine agonists; anti-inflammatory drugs; immunomodulators; statins; phytochemical agents and other compounds; PPAR ligands [49].

At the same time, the researchers have three main issues: the effectiveness of the treatment, the risk of drug resistance, and the possibility of side effects. The desired effect can be achieved by simultaneous inhibiting effects on several pro-angiogenic signaling pathway [50].

According to various authors, however, there is a risk of cumulative adverse effects by combining several drugs that inhibit angiogenesis [48–50]. Nevertheless, the concept of a combination of various inhibitors opens up new perspectives in the therapy of endometriosis.

Thus, treatment of endometriosis – medical and surgical – should be seen as complementary therapies. Personalized selection of the optimal medical and surgical component improves the efficiency of treatment and improves the prognosis.

**Conclusions**

Endometriosis is a disease that causes a severe pain in women of reproductive age. It increases neurogenesis in eutopic endometrium and in endometriotic heterotopia, as shown by the expression of a number of neurotrophins, their receptors, and increase of the nerve fibers density as compared with control tissues. Increase in the nerve fibers density and increased expression of various neurotrophins play a significant role in the formation of endometriosis-associated pain.

It requires further study of the pathogenetic basis of angiogenesis, lymphangiogenesis, and neurogenesis, which will develop new and effective methods of diagnosis, prevention, and treatment of disease.

Thus, many researchers believe that the study of angiogenesis, lymphangiogenesis, and neurogenesis allow us to find an innovative approach to the diagnosis of endometriosis. Therapy for endometriosis that is found on the principle of the translational medicine will effectively fight disease, improve quality of life of patients, and restore the endocrine and reproductive functions.

---

**Declaration of interest**

The authors report that they have no conflicts of interest.

**References**

1. Meuleman C. High prevalence of endometriosis in infertile women with normal ovulation and normospermic partners. Fertil Steril 2009;92:68–74.
2. Guo SW, Wang Y. The prevalence of endometriosis in women with chronic pelvic pain. Gynecol Obstet Invest 2006;62:121–30.
3. Fauconnier A, Chapron C, Dubuisson JB, et al. Relation between pain symptoms and the anatomic location of deep infiltrating endometriosis. Fertil Steril 2002;78:719–26.
4. Dai Y, Leng JH, Lang JH, et al. Anatomical distribution of pelvic deep infiltrating endometriosis and its relationship with pain symptoms. Chin Med J (Engl) 2012;125:209–13.
5. Howard FM. Endometriosis and mechanisms of pelvic pain. J Minim Invasive Gynecol 2009;16:540–50.
6. Nnoaham KE, Hummelshoj L, Webster P, et al. Impact of endometriosis on quality of life and work productivity: a multicenter study across ten countries. Fertil Steril 2011;96:366–73.
7. Yeung Jr P, Sinervo K, Winer W, Albee Jr. RB Complete laparoscopic excision of endometriosis in teenagers: is postoperative hormonal suppression necessary? Fertil Steril 2011;95:1909–12.
8. Carmeliet P, Tessier-Lavigne M. Common mechanisms of nerve and blood vessel wiring. Nature 2005;436:193–200.
9. Girling JE, Rogers PAW. Recent advances in endometrial angiogenesis research. Angiogenesis 2005;8:89–99.
10. Berkley KJ, Rapkin AJ, Papka RE. The pains of endometriosis. Science 2005;308:1587–9.
11. As-Sanie S, Harris RE, Napadow V, et al. Changes in regional gray matter volume in women with chronic pelvic pain: a voxel-based morphometry study. Pain 2012;153:1006–14.
12. Ma W, Tan J, Matsumoto H, et al. Adult tissue angiogenesis: evidence for negative regulation by estrogen in the uterus. Mol Endocrinol 2001;15:1983–92.
13. Bourlev V, Volkov N, Pavlovitch S, et al. The relationship between microvessel density, proliferative activity and expression of vascular endothelial growth factor-A and its receptors in eutopic endometrium and endometriotic lesions. Reproduction 2006;132:501–9.
14. Takehara M, Ueda M, Yamashita Y, et al. Vascular endothelial growth factor A and C gene expression in endometriosis. Hum Pathol 2004;35:1369–75.
15. Donnez J, Smeets P, Gillerot S, et al. Vascular endothelial growth factor (VEGF) in endometriosis. Hum Reprod 1998;13:1686–90.
16. McLaren J, Prentice A, Charnock-Jones DS, et al. Vascular endothelial growth factor is produced by peritoneal fluid macrophages in endometriosis and is regulated by ovarian steroids. J Clin Invest 1996;98:482–9.
17. Lee KF, Lee YL, Chan RWS, et al. Up-regulation of endocrine gland-derived vascular endothelial growth factor but not vascular endothelial growth factor in human eutopic endometriotic tissue. Fertil Steril 2010;93:1052–60.
18. Tariverdian N, Theoharides TC, Siedentopf F, et al. Neuroendocrine-immune disequilibrium and endometriosis: an interdisciplinary approach. Semin Immunopathol 2007;29:193–210.
19. Kalu E, Sumar N, Giannopoulos T, et al. Cytokine profiles in serum and peritoneal fluid from infertile women with and without endometriosis. J Obstet Gynaecol Res 2007;33:490–5.
20. Reichel S, Barcena De Arellano ML, Reichelt U, et al. Lymphangiogenesis in deep infiltrating endometriosis. Hum Reprod 2011;26:2713–20.
21. Yuan CL, Wang YS, Sheng H, et al. Expressions of insulin-like growth factor I and its receptor in endometriosis. J Clin Univ Med Ed 2007;33:567–9.
22. Loverro G, Maiorano E, Napoli A, et al. Transforming growth factor-beta 1 and insulin-like growth factor-1 expression in ovarian endometriotic cysts: a preliminary study. Int J Mol Med 2001;7:423–9.
23. Yoshida S, Harada T, Mitsuami N, et al. Hepatocyte growth factor/Met system promotes endometrial and endometriotic stromal cell invasion via autocrine and paracrine pathways. J Clin Endor Metab 2004;89:823–32.
24. Bourlev V, Larsson A, Olovsson M. Elevated levels of fibroblast growth factor-2 in serum from women with endometriosis. Am J Obstet Gynecol 2006;194:755–9.
25. Tokushige N, Russell P, Black K, et al. Nerve fibers in ovarian endometriomas. Fertil Steril 2010;94:1944–7.
26. Santamaria X, Massasa EE, Taylor HS. Migration of cells from experimental endometriosis to the uterine endometrium. Endocrinology 2012;153:5566–74.
27. Ellis A, Bennett DL. Neuroinflammation and the generation of neuropathic pain. Br J Anaesth 2013;111:26–37.
28. Szymanowski K. Apoptosis pattern in human endometrium in women with pelvic endometriosis. Eur J Obstet Gynecol Reprod Biol 2007;132:107–10.
29. Berbic M, Hey-Cunningham AJ, Ng C, et al. The role of FoxP3+ regulatory T-cells in endometriosis: a potential controlling mechanism for a complex, chronic immunological condition. Hum Reprod 2010;25:900–7.
30. Kyama CM, Overbergh L, Debrock S, et al. Increased peritoneal and endometrial gene expression of biologically relevant cytokines and growth factors during the menstrual phase in women with endometriosis. Fertil Steril 2006;85:1667–75.
31. Hapangama DK, Turner MA, Drury JA, et al. Sustained replication in endometrium of women with endometriosis occurs without evoking a DNA damage response. Hum Reprod 2009;24:687–96.
32. Aghajanova L, Hamilton A, Kwiatkiewicz J, et al. Steroidogenic enzyme and key decidualization marker dysregulation in endometrial stromal cells from women with versus without endometriosis. Biol Reprod 2009;80:105–14.
33. Tiberi F, Tropea A, Apa R, et al. Prokineticin 1 mRNA expression in the endometrium of healthy women and in the eutopic endometrium of women with endometriosis. Fertil Steril 2010;93:2145–9.
34. Hey-Cunningham AJ, Ng FW, Busard MPH, et al. Uterine lymphatic and blood micro-vessels in women with endometriosis through the menstrual cycle. J Endo 2010;2:197–204.
35. Bjorndahl M, Cao R, Nissen LJ, et al. Insulin-like growth factors 1 and 2 induce lymphangiogenesis in vivo. Proc Natl Acad Sci U S A 2005;102:15593–8.
36. Heishi T, Hosaka T, Suzuki Y, et al. Endogenous angiogenesis inhibitor vasohibin1 exhibits broad-spectrum antilymphangiogenic activity and suppresses lymph node metastasis. Am J Pathol 2010;176:1950–8.
37. Mechsner S, Weichbrodt M, Riedlinger WFI, et al. Estrogen and progestogen receptor positive endometriotic lesions and disseminated cells in pelvic sentinel lymph nodes of patients with deep infiltrating rectovaginal endometriosis: a pilot study. Hum Reprod 2008;23:2202–9.
38. Tokushige N, Markham R, Russell P, Fraser IS. Effects of hormonal treatment on nerve fibers in endometrium and myometrium in women with endometriosis. Fertil Steril 2008;90:1589–98.
39. Browne AS, Yu Sidell JN, Huang RP, Taylor RN. Proteomic identification of neurotrophic proteins in eutopic endometrium. Reprod Sci 2010;17:350A.
40. Wang G, Tokushige N, Russell P, et al. Neuroendocrine cells in eutopic endometrium of women with endometriosis. Hum Reprod 2010;25:387–91.
41. Polak G, Kwasniewski W, Barczyński B, et al. Low-Density Lipoproteins Oxidation and Endometriosis. Mediators Infl Amm. 2013;167–78.
42. SOGC Guideline – Endometriosis: diagnosis and management. Endometriosis. J Endometriosis 2010; 2: 207–8.
43. Practice Committee of American Society for Reproductive Medicine. Treatment of pelvic pain associated with endometriosis. Fertil Steril 2008; 90:260–9.
44. Vercellini P, Eskenazi B, Consonni D, et al. Oral contraceptives and risk of endometriosis: a systematic review and meta-analysis. Hum Reprod Update 2011;17:159–70.
45. Selak V, Farquhar C, Prentice A, Singla A. Danazol for pelvic pain associated with endometriosis. Cochrane Database Syst Rev 2007:CD000068.
46. Sasagawa S, Shimizu Y, Nagaoka T, et al. Dienogest, a selective progestin, reduces plasma estradiol level through induction of apoptosis of granulosa cells in the ovarian dominant follicle without follicle-stimulating hormone suppression in monkeys. J Endocrinol Invest 2008;31:636–41.
47. Attar E, Bulun SE. Aromatase inhibitors: the next generation of therapeutics for endometriosis? Fertil Steril 2006;85:1307.
48. Nawathe A, Patwardhan S, Yates D, et al. Systematic review of the effects of aromatase inhibitors on pain associated with endometriosis. BJOG 2008;115:818.
49. Djokovic D, Calhaz-Jorge C. Angiogenesis as a therapeutic target in endometriosis. Acta Med Port 2014;27:489–97.
50. Edwards AK, Nakamura DS, Virani S, et al. Animal models for antiangiogenic therapy in endometriosis. J Reprod Immunol 2013;97:85–94.