

# Neuroendocrine and stress-related aspects of endometriosis

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## Abstract

Endometriosis is a model of a benign gynecologic disease associated with two major symptoms: pain and infertility. When becomes chronic, severe psychological and neuroendocrine changes may occur. The high levels of perceived stress caused by symptoms cause a neuroendocrine disequilibrium thus contributing to the progression of the disease. Elevated stress levels alter hormonal secretions, mood and behavior, sexual disorders and appetite custom. Inflammatory comorbidities may be associated with elevated stress in endometriotic patients (inflammatory bowel disease, fibromyalgia, chronic fatigue) and even autoimmune diseases (thyroid disease, systemic lupus erythematosus, multiple sclerosis). Neurogenic mechanisms are described in endometriotic lesions and they affect peripheral and central nervous system of these patients increasing pain sensitivity and stress reactivity. In conclusion, endometriosis is a disease which affects reproductive and neuroendocrine functions with a great impact on women's health and quality of life.

## INTRODUCTION

Endometriosis is a benign gynecologic disease characterized by an increased estrogenic activity/progesterone resistance and by a chronic inflammatory state (Bulun 2009). The most commonly affected sites are the pelvic organs and peritoneum, although other parts of the body (muscle, liver, lungs) are occasionally affected. Three different clinical forms of endometriosis are considered: superficial peritoneal, ovarian, and deep endometriosis. In detail, superficial peritoneal endometri-

osis has multiple types of appearance; the typical lesion has a puckered, blue-black, powder-burned appearance, but also hemorrhagic (red vesicular or flamelike), or fibrotic (from white to black pigmented) lesions, may appear on peritoneum. Ovarian endometrioma (OMA) is also called a "chocolate cyst" because of the characteristic dark brown or chocolate-colored content; it may be mono or bilateral. Deep endometriosis (DE) is a specific entity histologically defined when endometriotic lesions extend more than 5 mm, underneath peritoneum. DE is responsible for the most

painful symptoms, the severity of which is strongly associated with the depth of the lesions.

Endometriosis is associated with infertility and pain (Giudice 2010). Pain occurs unpredictably and intermittently throughout menstrual cycle or it may also be continuous, exacerbated by physical activity (Morotti *et al.* 2014). The constellation of pain symptoms associated with endometriosis varies from person to person. Symptoms encompass an unspecified combination of dysmenorrhea, dyspareunia, and non-menstrual chronic pelvic-abdominal muscle pain the sentinel symptom being dysmenorrhea. Non menstrual chronic pelvic pain may persist for much of the month or only during specific times, such as at ovulation. Some women have additional painful symptoms such as dysuria, dysuria, dyschezia and other chronic musculoskeletal conditions, which may or may not be related to endometriosis. These pain symptoms and their chronicity patterns in relation with menstrual cycle and association with other types of visceral pain, ultimately reflect changing actions of nervous system. Pain in women with endometriosis often worsens over time and may change in character; infrequently, women report burning or hypersensitivity, symptoms that are suggestive of neuropathic component (Evans *et al.* 2007). Patients experience multiple symptoms associated with varying levels of distress, including symptoms not typically associated with endometriosis (Brawn *et al.* 2014). Some women with endometriosis suffer from chronic, disabling pain while others appear symptom free, independently of stage of disease, thus patients with mild disease suffer from severe symptoms, and vice versa (Morotti *et al.* 2014).

Important elements that influence pain experience are: affective state, attention, interpretations and beliefs about the pain itself. In addition, chronic pain might have a negative impact on both personal and social level, including loss of work ability, social activity limitations, lack of support from the family members and partner. Moreover, unclear prognosis, lack of illness-related information, or unpredictability of symptoms may result in uncertainty (Novella-Maestre 2009).

The experience of uncertainty is inherent in all chronic illness, the effects of which persist day after day, year after year. The great emotional distress associated with uncertainty leads women with endometriosis to a reduced quality of life (Nnoaham *et al.* 2011; Simoens *et al.* 2012). For all these reasons, in women suffering from endometriosis quality of life is reduced not only for the negative impact of the painful symptoms, but for more complex and multidimensional aspects. Different forms of endometriosis are associated with different level of stress perception suggesting a correlation between the severity of the disease and the intensity of the stress. Indeed, women with DE or DE+OMA showed the highest severity of dysmenorrhea, pelvic pain and dyspareunia strongly correlated with high level of stress perception and surgical treatment decreased both stress perception and pain score (Lazzeri *et al.* 2015).

The elevated levels of perceived stress suggests that chronicity of endometriosis strongly affects the mechanisms of stress in various extent, and that the correct management (medical and surgical) may improve the stress-related categories and the assessment of coping strategies, psychosexual treatment should be part of the management in women with long term history of endometriosis (Lazzeri *et al.* 2014).

Stress activates hypothalamus-pituitary-adrenal (HPA) axis. The continuous and prolonged activation of HPA axis causes the negative feedback loop to become deregulated, leading to either enhanced hormone production and release or resistance to circulating glucocorticoids (Blackburn-Munro 2003). Stress hormones affect chronic stress which in turn may cause chronic fatigue, psychiatric diseases, sexual disorders, all contributing to a reduced quality of life (Tariverdian 2007).

## STRESS HORMONES IN ENDOMETRIOSIS

A neuroendocrine disequilibrium in response to high levels of perceived stress caused by symptoms may occur in endometriosis, and may contribute to the progression of the disease (Tariverdian *et al.* 2007a; Kalantaridou *et al.* 2004). Stress reactivity and family relationships in women with endometriosis may contribute to development and recurrence of symptoms. Family history with chronically elevated levels of stress reactions might be considered as risk factors for endometriosis as well as the lack of contact between family members might magnify the levels and patterns of reactivity stress in women with endometriosis (Harrison *et al.* 2005).

Stress leads to the active release of hypothalamic corticotrophin-releasing hormone (CRH), pituitary ACTH and adrenal cortex glucocorticoids (GCs) accompanied by additional stress mediators like neuropeptides and immune mediators (Elenkov *et al.* 2010; Webster *et al.* 2005). In peritoneal fluid of women with endometriosis CRH and CRH-binding protein (CRH-BP) are increased in advanced stages of endometriosis (Florio *et al.* 1998). Also endometrial CRH expression results impaired in endometriosis (Novembri *et al.* 2011a).

Elevated serum cortisol levels are associated with stress and decrease pituitary-ovarian hormones regulating ovulation (Petraglia *et al.* 1987). High levels of cortisol and catecholamines, interacting with estrogen and progesterone in regulating tubal motility, and stress occurring during menstrual cycle may enhance tube reflux activity and endometrial cells reflux towards pelvis (Tariverdian *et al.* 2010b). Additionally, in chronic stress, loss of glucocorticoid receptor expression may cause a loss of glucocorticoid inhibition of pro-inflammatory cytokines that results in an increase in cytokine levels (Sapolsky *et al.* 2000). The resulting chain of events contributes to peripheral and central sensitization (Brawn *et al.* 2014). Clinical studies on chronic pain states such as fibromyalgia, rheuma-

toid arthritis and several autoimmune inflammatory diseases implicate involvement of dysfunctional HPA responsivity and the same situation likely applies to endometriosis and chronic pain (Crofford 2002). Adrenal medulla catecholamines are other stress hormones associated with pain and inflammatory disease, probably secreted even in the endometriosis inflammatory environment (Chrousos & Gold 1992).

Women with endometriosis have mild increase in serum prolactin levels (Wang *et al.* 2009). Since a dopamine receptor D2 polymorphism has been shown in women with moderate/severe endometriosis, it may be related with a defect in post-receptor signaling mechanism, resulting in a mild increase in serum prolactin levels (Wang *et al.* 2013). This altered mechanism might also contribute to the pathogenesis of endometriosis via the powerful induction of angiogenesis by prolactin which may induce or maintain endometriotic lesions (Novella-Maestre *et al.* 2009).

Growth hormone (GH) is increased in endometriosis tissue compared to normal uterine epithelial cells. This protein appear to be involved in the progression of the disease: it is known to not only promote cellular proliferation but also reduces cell-cell adhesion, thus allowing individual cells to break away from their parent architecture (Slater *et al.* 2006). In addition, recent paper showed a different GHRH and GHRH-SV1 expression among endometriotic tissue at different stages of endometriosis suggesting that GH may play a role in the progression of endometriosis (Wang *et al.* 2013).

## STRESS-RELATED DISORDERS IN ENDOMETRIOSIS

### Depression

Women with endometriosis show higher incidence of introversion anxiety, psychiatric disorders and depression compared to healthy women. The presence of the disease correlates with the presence of anxiety and depressive traits is often linked to dissatisfaction at work, socio-economic issues and with the presence of high psychosocial stress, impairing work, social, and family functioning, with no correlations between the severity of disease and level of mental discomfort (Centini *et al.* 2013).

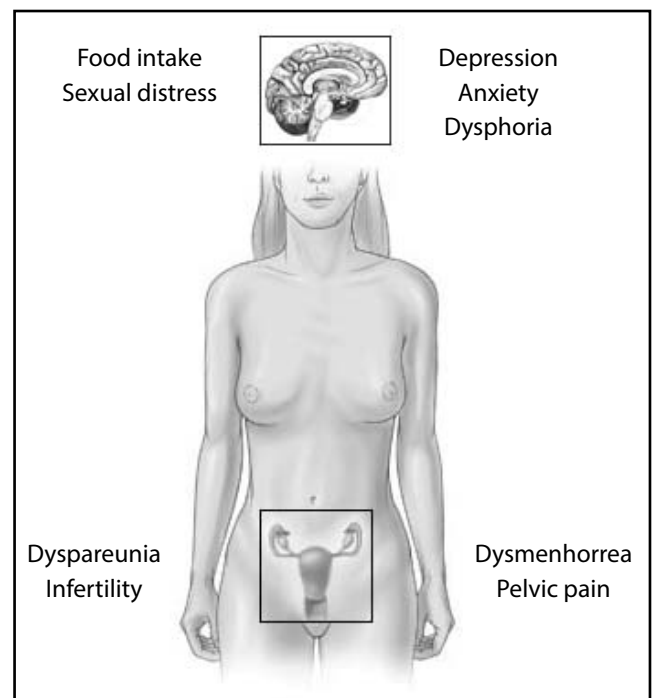
Endometriosis-related pain is consistently reported as a central and destroying component of life in women with endometriosis and several studies report a negative correlation between pain and quality of life, including productivity at work, causing limitations in ability to perform work-related activities and decrease in the quality of work, up to the job loss (Bernuit *et al.* 2011). Among Brazilian women with endometriosis, depression was found in 86% of those with chronic pelvic pain, compared with 38% of those without such pain (Loren-catto *et al.*, 2006). Women with symptomatic endometriosis present greater depression and more often suffered

from sexual dysfunction, but endometriosis itself may be responsible for mental suffering among women studied (De Sepulcri & do Amaral 2009).

Symptoms of depression include dysphoria, anhedonia, and dysregulation of appetite, sexual behavior and sleep. Depression is indeed a common psychological reaction to chronic pain and illness is related to feelings of loss and lack of control. Anxiety includes phobias and panic disorders, as well as feelings of fear and uneasiness. Patients with endometriosis may have fears and concerns about the future consequences of the disease (Eriksen 2008). These concerns might worsen mood and mental disorders especially if associated to infertility (Centini *et al.* 2013).

The experience of infertility leads to a crisis which threatens self-esteem, self-confidence, sexual identity which can then be followed by secondary affective and somatoform disorders. For many patients infertility is synonymous with the destruction of a life concept and also a concept of themselves. This threat of remaining childless is aggravated by the challenge of entering early menopause (Bitzer 2001).

A role of counseling and psychosomatic care has been suggested by teaching patients about endometriosis and its multidisciplinary treatment, guiding women through the sometimes complicated treatment of infertility, providing written information, and/or sharing educational videotapes or electronic resources may enhance women's knowledge and reduce uncertainty and emotional distress associated with endometriosis (Bitzer 2001; Huntington & Gilmour 2005) (Figure 1).



**Fig. 1.** Mood and affective disorders occurring in women with endometriosis.

### Sexual disorders

Another aspect that negatively influences women with endometriosis is dyspareunia, a common symptom of the disease, four times more frequent in women with endometriosis than in controls and five times more frequent in patients with peritoneal endometriosis than in those with endometriotic cysts (Olive & Pritts 2001). Dyspareunia is severe before menstruation and is also associated with infiltrating endometriotic lesions of the uterosacral ligaments (Porpora *et al.* 1999) and/or with traction of scarred inelastic utero-sacral ligaments during sexual intercourse (Olive & Pritts 2001).

Women with endometriosis try to cope with the sexual complaints, either to satisfy the partner or to conceive. Hence, they sacrifice their own pleasure and had sexual intercourse despite pain with the focus on the partner's pleasure instead of themselves. Not surprisingly, more than half of women (66%) were afraid of pain before/during sexual intercourse. Thirty-eight out of 125 patients (30%) had a sexual dysfunction and sexual distress simultaneously. Only 21% of women had none of these disorders. A significant association was found between female sexual distress and previous sexual abuse. These feelings of fear can lead to physical tension and therefore no relaxation and fulfillment is possible. As a consequence, negative emotions towards themselves, feelings of guilt towards the partner, the opinion of being an insufficient partner and fear of breaking up the relationship were predominant. It is very important, therefore, that gynecologists involved in the management of endometriosis offer patients a profound conversation about their sexuality, because these professionals in most cases are the first reference persons for suffering women. Due to the fact that sexuality (especially impaired sexuality) is often a shameful topic, it is the task of the gynecologist to address this delicate issue in a pleasant way (Fritzer *et al.* 2013). This is the reason why more attention should be put on psychological profile of a woman suffering from endometriosis and on her quality of life (Vercellini *et al.* 2014).

### Eating disorders

Body weight changes and eating disorders have to be considered in endometriosis. During childhood and early adulthood the influence of body weight is critical, since body size around the time of menarche is more relevant than body at the time of diagnosis (Vitonis *et al.* 2010). In a large group of diagnosed endometriosis, BMI at age 5, 10 and 20 was inversely associated with laparoscopically confirmed endometriosis. Compared with the mean body size at the age 5, there was a 23% increased risk for endometriosis among the most lean and 10% decreases risk for the most overweight. The associations at age 10 and 20 is similar. A decrease in body size from ages 5–20 and 10–20 is associated with increases risk. Thus factors that may alter estrogen status such as age at menarche and BMI may influence the incidence of endometriosis (Apter *et al.* 1989).

Moreover, body size might influence HPA axis function since. Women with anorexia nervosa have increased activity of HPA axis, with high cortisol awakening response in women (Lawson *et al.* 2009). Moreover, stress mechanisms are altered in these women leading to an impaired immune response, in fact TNF-alpha and oxidative stress are higher in women with anorexia (Agnello *et al.* 2012). Therefore, the lower BMI in women with endometriosis and the impaired stress response are strictly connected and might contribute to the pathogenesis of the disease.

Indeed a low BMI in adulthood is associated with an increased risk of DE (Lafay Pillet *et al.* 2012). A possible role of leptin in endometriosis is suggested by the elevated levels in peritoneal fluid of women with endometriosis (Kitawaki *et al.* 2000), affecting immune cells and cytokines (Milewski *et al.* 2008; Styer *et al.* 2008; Wu *et al.* 2010) as well as influencing metabolic determinant of BMI (Wagner *et al.* 2012). Overweight girls experiencing earlier menarche do not increase the risk of developing the diseases (Cramer *et al.* 1986; Missmer *et al.* 2004a; Missmer *et al.* 2004b), probably because hyperinsulinemia, insulin resistance and lower levels of sex hormone-binding-globulins (SHBG) in obese girls may be protect from the disease (Baer *et al.* 2007).

As consequence diet may play a role in the establishment and progression of endometriosis (Parazzini *et al.* 2013a), because diet may affect inflammation, estrogen activity, menstrual cycle and prostaglandin metabolism (Missmer *et al.* 2010c). Specific habitual dietary have a moderate influence on some inflammatory markers, increased in endometriosis (Galland 2010). There is an inverse association between vegetables and fruit intake and the risk of several conditions has been one of the most common reported factors in dietary epidemiology (Masala *et al.* 2012). Green vegetables and fruit consumption are inversely associated with the risk of endometriosis (Parazzini *et al.* 2004b). Omega 3-fatty acids show an inhibitory effect on inflammation mediator secretion suggesting an important therapeutic role in the control of pelvic pain (Novembri *et al.* 2011 b). In an opposite manner, red meat and saturated fat are associated with elevated estradiol and estrone sulphate concentrations and its consumption might directly contribute to human circulating steroid hormone concentrations and ultimately to the disease maintenance (Andersson *et al.* 1999).

## **AUTOIMMUNE DISORDERS IN ENDOMETRIOSIS**

Inflammation and endometriosis are linked and confirmed by the high serum levels of IgG, IgA, IgM and antiendometrial antibodies and the high prevalence of autoimmune diseases in women suffering with endometriosis. Of the co-morbid diseases, fibromyalgia and chronic fatigue syndrome are the most common reported associations (Sinaii *et al.* 2002; Gleicher *et al.*

1987; Grosskinsky & Halme 1993). The autoimmune inflammatory diseases systemic lupus erythematosus, systemic sclerosis, rheumatoid arthritis and multiple sclerosis occurred more frequently in women with endometriosis than in general population (Meek *et al.* 1988; Nielsen *et al.* 2011; Notchnick 2001).

In women with endometriosis the rate of allergies and other atopic conditions is also increased. Indeed, women with endometriosis show an increased risk of inflammatory bowel disease (IBD) and irritable bowel disease (25%) more than general population (Jess 2012). Both endometriosis and IBD are chronic inflammatory disorders with typical onset in young adulthood and do not only share immunological alterations, but also affect the bowel and may cause abdominal pain. Also migraine and menstrual headaches are more common in women with endometriosis (Smorgick 2013). The co-presence of endometriosis and interstitial cystitis (66%) in women with chronic pelvic pain is described and inflammatory characteristics suggest a possible correlation (Paulson & Delgado 2007; Butrick 2007).

Autoimmune thyroid diseases are associated with endometriosis. The overall frequency of thyroid dysfunction may be compared with healthy women, without significant differences (Petta 2007) but other reports show a high prevalence of hypothyroidism in women with endometriosis (Sinai *et al.* 2002). The early onset of thyroid disease and rheumatoid arthritis, as well as the higher rate of autoimmune inflammatory diseases, supports the hypothesis of an immunological aspect to endometriosis.

In conclusion, women with endometriosis frequently suffer from inflammatory and autoimmune diseases, hypothyroidism, fibromyalgia, chronic fatigue syndrome, allergies and asthma. It is evident that women with pelvic pain are often not diagnosed as having endometriosis for many years, suggesting that physicians should consider this diagnosis. These data suggest a strong association between endometriosis and autoimmune disorders and indicate the need to consider the coexistence of other co-morbid conditions in women with endometriosis (Figure 2).

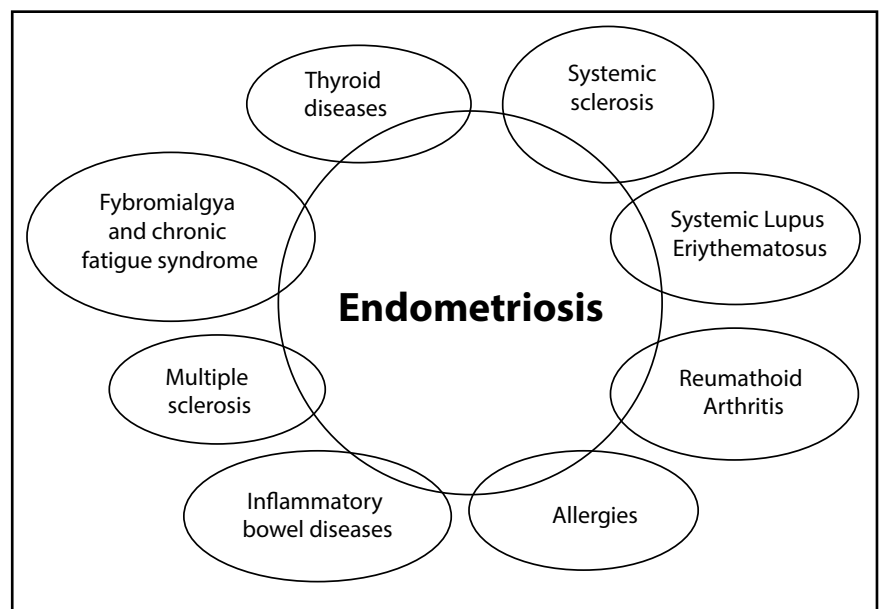
Other neuroendocrine aspects of endometriosis

The most striking evidence of neuroendocrine role of endometrium of endometriosis is the presence of multiple small unmyelinated nerve fibers in the eutopic endometrium of women with laparoscopically confirmed endometriosis, but not in the endometrium of women without endometriosis (Tokushige *et al.* 2006a; Tokushige *et al.* 2007b),

in suggesting an important role in the genesis of pain. It is not known what conditions or molecular stimuli may attract nerve fibers to grow into the eutopic endometrium in women with endometriosis. Eutopic endometrium in patients with endometriosis is innervated by A $\delta$  and C sensory fibers and adrenergic fibers and that the myometrium in patients with endometriosis is innervated by A $\delta$  and C sensory, adrenergic, and cholinergic fibers, these fibers being denser than those in women without endometriosis (Tokushige *et al.* 2008c). A significant reduction in the density of nerve fibers following hormonal therapy in eutopic endometrium and in myometrium of endometriosis correlates with reduced pain in these patients (Bokor *et al.* 2009).

Recent studies of endometriotic lesions revealed the presence of sensory nerve fibers as markers for nociception. Endometriosis associated pelvic pain appears to be due to nociceptive, inflammatory, oxidative stress, angiogenic, neurovascular, or neuropathic mechanism (Morotti *et al.* 2014). Nerve fibers are thought to play central roles in the generation of pelvic pain and neuronal growth in women with peritoneal endometriosis, ovarian endometriosis and DE (Zhang *et al.* 2010). DE lesions have multifocal pattern of distribution, especially in the uterosacral ligament and the cul-de-sacs and are significantly associated with severe pain symptoms.

Prostaglandins produced by postganglionic neuron terminals are associated with the genesis of hyperalgesia. These neuron fibers appear to be involved in the generation of pain symptoms (Tokushige 2006d). Thus, causes of neuropathic pain are associated with excessive inflammation. The endothelial cells activated by mechanical stimulation contribute to hyperalgesia through a nociceptive effect of endothelin-1 (ET-1) in a model of endometriosis (Joseph *et al.* 2013).



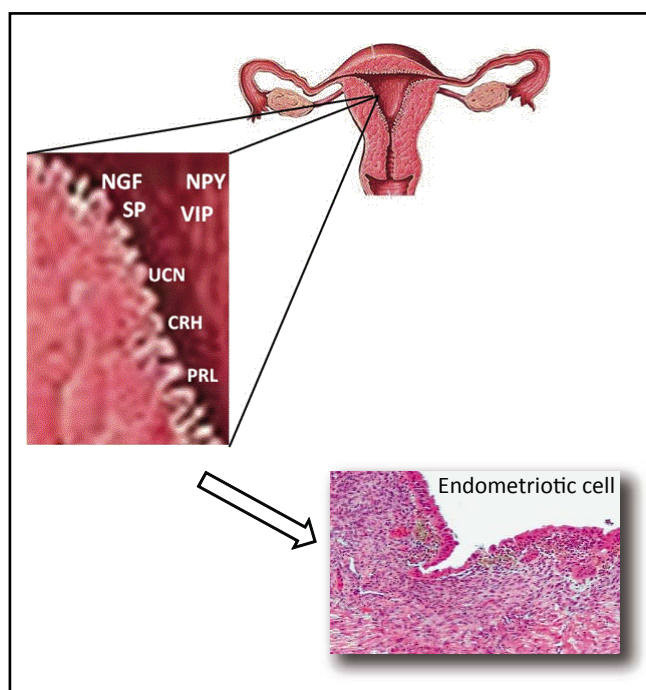
**Fig. 2.** Inflammatory and autoimmune comorbidities in endometriotic patients.

Nerve fibers in peritoneal endometriosis contain unmyelinated sensory C, myelinated sensory A $\delta$  and adrenergic nerve fibers (Tokushige *et al.* 2006d). Recent studies have confirmed an increased sensory and a decreased sympathetic nerve fibers density in peritoneal endometriotic lesions as compared to healthy peritoneum. Ovarian endometrioma was also innervated by mainly sensory and sympathetic fibers (Arnold *et al.* 2012). The nerve fiber density was higher in DE than in peritoneal endometriosis. Entrapment of nerve fibers within the inflamed endometriotic nodules may represent a possible mechanism explaining the severity of pain (Chapron *et al.* 2003). An increase in functional sensory nerve fibers may be correlated with the severity of pain in women with endometriosis (Zhang *et al.* 2010). Increased nociceptive input can stimulate neurons that receive convergent input from primary afferents to the dorsal root ganglion. The presence of endometriosis-associated functional nerve fibers appears to be related to the pelvic pain.

Expression of genes related to nerve fibers growth was up-regulated in eutopic endometrium of women with endometriosis in comparison with those without endometriosis (May *et al.* 2011). Transient receptor potential vanilloid 1 (TRPV1) and transient receptor potential ankyrin 1 (TRPAk) are two critical types of TRP channels that selectively act as nociceptors (Caterina *et al.* 2000). They are strongly implicated in the genesis of peripheral neuroinflammatory pain (Liu *et al.* 2012). The production of proinflammatory cytokines from endometriotic lesions and immune cells might be responsible for the excessive sensory innerva-

tions and modulation of sensory pain activity (Santanam *et al.* 2013) (Figure 3).

Other studies have shown that there are numerous peritoneal blood vessels surround active endometriotic lesions, and the implant itself is also endowed with a rich vascularized area; this can be observed under histological examination and confirms the essential role that angiogenesis plays in the development and continuation of endometriotic lesions. In these studies it has been observed that human endometrium engrafted in immunocompromised mice promotes the growth of neovessels from the surrounding host vascular network in order to provide the endometriotic lesions with an adequate blood supply. Studies in a experimental mouse model of endometriosis have shown that the dopamine agonist (DA), cabergoline (cb2), reduces angiogenesis in endometriotic lesions, hypothetically binding to the dopamine receptor type-2 (DRD2) (Delgado-Rosas *et al.* 2011). The dopamine agonist cabergoline (cb2) inhibits the growth of established endometriosis lesions by exerting antiangiogenic effects through VEGFR2 inactivation. However, the use of ergot-derived Cb2 is associated with an increased incidence of cardiac valve regurgitation. Pellicer *et al.* hypothesized that dopamine receptor 2 (DRD2) agonists (DRD2-A) could be an alternative to commercial antiangiogenic agents. In animal models, DRD2-A inhibits pathologic angiogenesis in tumors by inactivating VEGFR2 signaling. They have previously used a well-established experimental endometriosis model to demonstrate that the DRD2-A cabergoline (Cb2) prevents the formation of typical endometriosis lesions by inhibiting angiogenesis. These results encouraged to perform a pilot study to evaluate the efficacy of Cb2 in the treatment of peritoneal endometriosis in humans (Delgado-Rosas *et al.* 2011). Neuroactive factors are present in eutopic endometrium of women with endometriosis that may have effects on nerve fiber growth. They include nerve growth factor, neuropeptide Y (NPY), substance P (SP), neurotensin, and vasoactive intestinal peptide. Indeed, eutopic endometrium in women with endometriosis has been found to have a higher of NPY, VIP and SP than in women without endometriosis (Tokushige *et al.* 2007b) (Figure 3).



**Fig. 3.** Endometrial neuropeptides possibly involved in the mechanisms of endometriosis.

## CONCLUSIONS

Endometriosis remains a prevalent condition in women of reproductive age, characterized by the presence of endometrial tissue in extra-uterine sites, including the ovaries and other pelvic structures. Endometriosis is a disease which primarily affects reproductive function but has also a great impact of quality of life. Pain symptoms, neuroendocrine factors, and impaired stress response, mood and behavior states are associated with chronic inflammation and impaired immune function. Leading to a chronic fatigue state and depression. A neuroendocrine disequilibrium in response

to high levels of perceived stress caused by symptoms may occur in endometriosis and may contribute to the progression of the disease. Stress reactivity and family relationships in women with endometriosis may contribute to development and recurrence of symptoms or to stability and recovery from symptoms.

Women with endometriosis show higher incidence of introversion anxiety, psychiatric disorders and depression compared to healthy women. Another aspect that negatively influences women with endometriosis is dyspareunia, a common symptom of the disease which has a negative effect on sexual. Body weight changes and eating disorders have to be considered in endometriosis. Women with endometriosis frequently suffer from autoimmune inflammatory diseases, hypothyroidism, fibromyalgia, chronic fatigue syndrome, allergies and asthma. In conclusion, endometriosis is a disease which affects reproductive and neuroendocrine functions with a great impact on women's health and quality of life.

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