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Review Article

Endometriosis Therapy: Not Only Hormones and Surgery - The Importance of a Holistic Approach

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Abstract

Endometriosis is a pathology that affects just under 10% of women of reproductive age and is characterized by symptoms, sometimes very severe, which manifest themselves as dysmenorrhea, dyspareunia and chronic pelvic pain. Many women with this disease are also infertile. To date, there is no therapy that cures the woman who is affected by it. Hormonal therapies and surgery tend to cure the symptoms and slow down the course until menopause, a period in which, in the vast majority of cases, the disease resolves itself. The Authors intend to evaluate, through the review of the literature and the experience of "insiders", a range of therapeutic forms that do not want to replace hormonal treatments or surgical techniques, which are still the subject of discussion, but which aim to support of these to try to make the life of women with endometriosis the best possible. Thus, a new concept was born for the Authors on how to deal with endometriosis: the concept of "holism" which leads us to evaluate this pathology in a complex of therapeutic globality, without excluding a priori ways of treatment wrongly considered ineffective and therefore "not officers". We will address the concepts of adequate nutrition associated with the use of supplements and antioxidants, with the help offered by osteopathy, fitness, ozone therapy, acupuncture, up to the psychological support.

Keywords: Endometriosis, Nutrition, Oxidative stress, Ozone therapy, Fitness, Osteopathy, Acupuncture, Psychology

Introduction

Endometriosis is one of the most common benign disorders, affecting 6-10% of women of reproductive age [1]. The disease is defined as the presence of endometrial glands and stroma outside the uterine cavity, and patients with endometriosis often suffer from dysmenorrhea, dyspareunia, dysuria, and chronic pelvic pain. About 50% of these patients are infertile. Since the disease is estrogen-dependent, medical therapies primarily aim to down-regulate ovarian estrogen production [2]. Endometriosis is a chronic disease, characterized by pain of varying intensity, often diagnosed late. Chronicity in itself indicates a pathological situation from which one will never fully recover, but this does not mean that physical symptoms, anxiety or psychological discomfort cannot be effectively treated by different forms of therapy. Pelvic pain associated with endometriosis can be treated medically and surgically. Surgery, however conservative it may be, removes the disease (although complete eradication is sometimes impossible) but increases the risk of compromising the ovarian reserve and damaging affected or adjacent anatomical structures. The risk of postoperative recurrences is high [3]. First-line medical treatments affect hormonal status by inducing a hypoestrogenic environment. Commonly used drugs are combined oral contraceptives and progestogens. Gonadotropin agonists and antagonists

are also used, but only for short periods because they are burdened with serious side effects such as bone loss. These therapies are often limited by their high cost and frequent side effects [4]; furthermore, they all have a contraceptive effect which does not go well with the fact that the disease affects young women often with a high desire for pregnancy. The real problem is that after discontinuation of therapy the disease becomes active again and pain scores often return to baseline values. About 50% of women with endometriosis experience a recurrence of symptoms within 5 years, regardless of the therapeutic approach [5]. Non-hormonal therapies are limited to non-steroidal anti-inflammatory drugs (NSAIDs) whose effectiveness is very limited and can have important side effects, especially if used for a long time [6].

The term "holism" comes from a Greek term for "integrity". Holism in medicine represents a "global" state of health, the union of mind, body, environment and society. The holistic approach considers the health and care of the patient as a whole, including their physical, psychological, social and spiritual well-being as they are not aligned with a specific philosophy of care, starting from the awareness that "everything is more than sum of its parts". A holistic approach therefore establishes the need to intervene on the person through several parallel plans, but with a single purpose: a state of real and all-encompassing well-being [7]. It should be emphasized again that, to date, there is no therapy capable to care endometriosis. It is therefore important to continue to search for new safe and effective long-term treatments [8] and to evaluate all those supportive therapies that allow the woman who is affected to experience the disease in the best possible way. It is not the authors' intention to claim that the so-called "non-official" or "alternative" treatments can effectively replace hormonal and/or surgical therapy. The intention is to explore other therapeutic avenues that can support the "official" therapy in the treatment of endometriosis.

Diet

According to the latest Australian national online survey, as many as 76% of women with endometriosis use non-pharmacological practices and lifestyle choices such as relaxation techniques, movement and nutrition. Nearly half of the women managed dietary support and diet effectiveness had high self-reported improvement scores [9]. In recent years, an increasing number of endometriosis patients have focused on dietary factors that promote health and support therapy [10].

Diet is a highly controllable risk factor for many chronic diseases, and its role as a contributor to endometriosis has been extensively explored. A literature review conducted by *Parazzini, et. all*. [11] suggested that women with endometriosis appear to consume fewer vegetables and omega-3 polyunsaturated fatty acids while consuming higher amounts of red meat, coffee, and trans fats (not those found naturally in foods but those added artificially to sweet and savory snacks). of industrial production). Red meats and butter intake are considered the primary sources for saturated fat. In an Italian case-control study [11] the risk of endometriosis was significantly higher in women who reported a higher consumption of meat and ham but not butter. These data contrasted with a Belgian clinical case-control study [12] which indicated that the consumption of butter, but not meat, was marginally associated with the risk of peritoneal endometriosis. However, it should be emphasized that a high intake of red meat is associated with discrete concentrations of estradiol and estrone sulphate [13] and, consequently, its consumption could directly contribute to increasing the levels of circulating human steroid hormone and therefore to the maintenance of the disease. The intake of monounsaturated fats (olive oil, whole milk products, nuts, lard, sesame oil, corn oil, popcorn, whole grains and wheat cereals) does not appear to have any association with the risk of endometriosis [14]. Olive oil is an important source of micronutrients and a wide variety of valuable antioxidants not found in other oils. The high content of oleic acid makes olive oil not very susceptible to oxidation. This oil also contains phenols which are believed to be powerful scavengers of superoxide and other reactive species [15].

Dairy products are an important part of the diet because they are rich in many amino acids and have a high calcium content. Studies have shown that dairy products, like products that contain high amounts of calcium, are negatively correlated with inflammatory and oxidative stress [16]. Altura and coll. [17] hypothesized that the high levels of magnesium contained in dairy products would relax the smooth muscles of the salpinges with a consequent reduction of retrograde menstruation, which according to many authors lies at the basis of the pathogenesis of endometriosis. Therefore, some researchers have speculated that intake of dairy products

might reduce the risk of endometriosis, but this hypothesis is based on limited studies and needs further testing. *Xiangying, et al.* [17] conducted a systematic meta-analysis to investigate the association between dairy products, and their amount in the daily diet, and the risk of endometriosis. The meta-analysis involved 120,706 participants and showed that the total intake of dairy products would reduce the risk of endometriosis with a dose-dependent relationship. The health benefits of green tea, red wine, garlic and fresh fruit and their effectiveness in preventing various diseases has been confirmed by several studies [18]. Catechins in green tea and polyphenols in red wine are products that are part of our daily food habits and have demonstrated many beneficial effects. Epigallocatechin-3-gallate (EGCG) is the main catechin found in green tea and has been studied in recent years for the treatment of various types of cancer, based on its antioxidant, antiangiogenic and antiproliferative effects. Its antimitotic properties have led to the idea that EGCG may be useful for the treatment of endometriosis. Recent studies have shown encouraging results in this area [19].

Another compound whose efficacy has been studied is resveratrol, a natural phytoalexin produced by some grape varieties, peanuts and berries in response to fungal infections or UV radiation. The most significant concentrations of resveratrol are found in grape skins and therefore in red wines. Evidence indicates that this compound has anticancer, anti-inflammatory, and antioxidant properties as well as pro-apoptotic and antiangiogenic effects [20]. Bruner-Tran and coll. evaluated the effect of resveratrol on experimental endometriosis in vivo and on the invasiveness of endometrial stromal cells in vitro [21]. Resveratrol reduced the number of endometrial implants per mouse by 60% ($P < 0.001$) and the total lesion volume per mouse by 80% ($P < 0.001$). These observations may aid in the development of new endometriosis treatments. Similar results were achieved by the experimentation of *Ricci, et al.* [22,23], performed on 56 female BALB/c mice, inducing endometriotic-like lesions and then treating them for 4 weeks with resveratrol and EGCG. The number of confirmed lesions observed per mouse was significantly reduced. The volume of lesions developed also decreased in statistically significant way. The reduction in both the number and size of the induced lesions is due to a decrease in epithelial cell proliferation and a significant increase in the apoptotic index. An inhibitory effect of vascular proliferation has also been shown by reducing the levels of VEGF in the peritoneal fluid.

The Supplements

Dietary supplementation has friends and enemies.

The basic concept lies in becoming aware that the industrial revolution has led to an increase in the supply of food products, but large-scale production has been detrimental to the quality of food. Pollution and radiation have depleted the soils of 50% of nutrients. Therefore, correct food supplementation, which completes what is missing from our diet today, however well-groomed, and correct, will allow our body to recover those nutrients which unfortunately it is currently no longer able to obtain in the right quantity from food. The President of the Mario Negri Institute, dr. Silvio Garattini, on the contrary, maintains that never as in recent decades has there been an abundance of food in industrialized countries, often high in protein and high in calories, which is the basis of obesity, which is on the alarming increase. Therefore, the use of food supplements is limited to the prevention of malnutrition by default. Their alleged health value in promoting physical well-being, delaying aging and reducing the risk of developing certain well-being pathologies (cardiovascular or metabolic diseases as well as some neoplasms) is to be demonstrated.

We will limit ourselves to indicating those supplements that can help improve the well-being of women with endometriosis.

Omega 3

It's important to remind that endometriosis is a chronic inflammatory disease and it's therefore correct to focus on the purposes of inflammation, which is a physiological process, aimed at guaranteeing the integrity of the organism, and is triggered by harmful stimuli such as pathogenic microorganisms and tissue damage [24]. The purpose of inflammation is twofold: it intervenes to contain or eliminate the factor determining the damage by preventing its spread and activate the repair processes of damaged tissues for the restoration of tissue homeostasis [25]. Cortisone anti-inflammatory drugs and NSAIDs often have too aggressive an action with negative consequences such as dysregulation of the immune response, gastro-intestinal pathologies and alterations in renal function.

Omega-3 fatty acids are a category of essential polyunsaturated fatty acids which, as demonstrated by recent studies, have an anti-inflammatory and antioxidant action, contributing to the formation of inflammatory mediators such as prostaglandins and leukotrienes. It is in fact important to modulate inflammation in order to respect its physiological role of maintaining homeostasis and tissue integrity and, at the same time, preventing it from becoming chronic. In this context, proresolvins have a prominent place which are lipid mediators derived from polyunsaturated fatty acids that work as "agonists of inflammation resolution", they stimulate the specific and natural processes of resolution, not always perfectly functional, facilitating the return to tissue homeostasis until healing [26,27]. Kumar demonstrated that proresolvins are able to counteract the progression of endometriosis [28]. Lipoxin A4 is recognized as an estrogen receptor agonist. The Author observed that a local treatment leads to the reduction of endometriotic lesions through the production of proinflammatory interleukins, the reduction of VEGF, the modulation of COX and MMP-9.

Melatonin

Starting from the observation that pinealectomy had induced a worsening of endometriotic lesions in rats and that the administration of melatonin had reversed this effect [29], we began to study more fully the correlation between this hormone and endometriosis. Schwertner in 2013 [30] with a randomized controlled, double-blind study, demonstrated that melatonin therapy (10 mg/day), in women with endometriosis, reduced overall pain scores by 39.8% and the use of analgesics by 80% after 8 weeks of treatment. Subsequently we investigated [31] the expression of the melatonin receptor in the eutopic endometrium of healthy women and in the eutopic and ectopic endometrium of women with surgically proven endometriosis. The study data demonstrated that the endometrium and endometriotic lesions possess an intact melatonin receptor signaling pathway and that this inhibits estradiol-induced cell proliferation, supporting the hypothesis that the use of melatonin can be used as an adjuvant therapy. in the management of endometriosis, even if the different receptor expressions indicate differences in efficacy between peritoneal and ovarian pathology.

Vitamin D

The serum level of vitamin D in women with unilateral ovarian endometriomas has been studied [32] and in particular the possible correlation between the size of the endometriomas and the serum levels of the vitamin has been evaluated. Hypovitaminosis D was diagnosed in 85.7% of the women investigated with a significant linear correlation with the diameter of the ovarian endometriomas: in the "hypovitaminosis D women", the mean diameter of the endometrioma was 40.2 ± 22.6 mm, while in "women with normal serum vitamin D levels" it was 26.7 ± 12.1 mm ($p = 0.1$). *Miyashita, et al*. [33] in 2016 isolated human endometriotic stromal cells (ESCs) isolated from ovarian endometriomas and cultured with 1,25(OH)2D3. They demonstrated that in vitro 1,25(OH)2D3 significantly reduced IL-1 or TNF-induced inflammatory responses, such as IL-8 expression and prostaglandin activity. 1,25(OH)2D3 also reduced the number of viable endometriotic cells and their DNA synthesis but did not affect apoptosis. Serum levels of the vitamin were also significantly lower in women with severe endometriosis than in controls and women with mild endometriosis. The Authors concluded, indicating vitamin D as a modulator of inflammation and proliferation in endometriotic cells, that a state of hypovitaminosis is associated with endometriosis, thus arguing that supplementation with Vit. D could be a new therapeutic strategy for endometriosis management.

Nickel

Gastrointestinal symptoms such as abdominal pain, bloating, constipation, and diarrhea are common in endometriosis and also tend to worsen during menstruation [34]. In endometriosis, there is inflammatory activity with both systemic and focused effects in the intestinal wall. A visceral sensitization occurs which leads to an intense sensation of pain and which contributes to the manifestation of "Irritable Bowel Disease" (IBS) [35]. Gastrointestinal symptoms in endometriosis may also be due to an alteration of the enteric nervous system, which is responsible for the control of muscular and secretory activity of the intestinal tract, reproductive tract and urinary tract [36]. In this complex neural system, any gastrointestinal inflammatory stimulus in the pelvic area can affect the functioning and

responses of other organs and in reverse. What Malin [37] defines as "cross-reactivity" takes place. In the more specific case of "deep infiltrating endometriosis" in the posterior compartment, in which the endometrial cells infiltrate the intestine, the symptoms are accentuated both by the local inflammation mediated by the prostaglandins but above all by the mechanical obstruction and/or microhemorrhages applicants [38]. Recent studies have shown a higher prevalence of nickel (Ni) skin allergy in women with endometriosis, supporting a possible involvement of nickel in its etiopathogenesis [39,40]. On this basis it is possible to hypothesize that an IBS-like disorder, such as allergic contact mucositis, (Ni ACM), may be the cause or a contributing factor to gastrointestinal symptoms in women with endometriosis. The high prevalence of Ni ACM in endometriosis and the relief from symptoms after a low Ni diet should lead us to suggest such a diet to this category of patients [41].

Antioxidants

Oxidative stress is a concept introduced for the first time in Denham Harman's theory in 1956 [42]. The term "Oxidative Stress" indicates the set of alterations that occur in tissues, cells and biological macromolecules when they are exposed to an excess of oxidizing agents. A state of oxidative stress results from the action of highly reactive unstable chemicals and ionizing radiation [43]. Free oxygen radicals (ROS) are reactive oxygen species, mainly produced by mitochondria, and are generated as metabolic byproducts by biological systems [44]. Processes, such as protein phosphorylation, activation of various transcription factors, apoptosis, immunity, and differentiation all depend on proper production and low-level presence of ROS within cells [45]. When ROS production increases, damaging effects occur on important cellular structures such as proteins, lipids, and nucleic acids. The cells implement a defensive antioxidant system [46] such as superoxide-dismutase, catalase and glutathione peroxidase and increase the use of vitamins E and C, in order to limit the production of ROS, inactivate and eliminate them, thus repairing the cellular damage [47]. It is now widely accepted that oxidative stress may be implicated in the pathophysiology of endometriosis by causing a general inflammatory response in the peritoneal cavity [48]. Macrophages, erythrocytes and apoptotic endometrial tissue, which are transplanted into the peritoneal cavity through retrograde menstruation, are inducers of oxidative stress. In fact, activated macrophages play an important role in the degradation of erythrocytes that release pro-oxidant and pro-inflammatory factors such as heme and iron, implicated in the formation of ROS [49,50].

Endometriosis, therefore, is considered as a complicated chronic inflammatory process associated with an increase in oxidative stress markers [47]. *Ngo, et al*. [51] found that a significant increase in endogenous oxidative stress biomarkers induces proliferation of endometriotic cells with disease progression. The authors found that patients with endometriosis have lower levels of antioxidants, such as vitamin A, vitamin C and vitamin E, in the follicular fluid of mature oocytes before ovulation. These low levels reflect the reproductive performance of the oocytes. Thus, an imbalance in the production of ROS in the follicular fluid of women with endometriosis could lead to a negative effect on oocyte quality, implantation, and embryonic development [52], justifying the high incidence of infertility. They then demonstrated that Vit C supplementation for 2 months (1 g/day) improved the quality of the oocytes and the embryo. A previous study [53] demonstrated that supplementation with antioxidant vitamins (Vit E and Vit C) led to a significant decrease in peritoneal fluid concentrations of inflammatory factors and a reduction in chronic pelvic pain in women with endometriosis.

Ozone Therapy

Ozone (from the Greek *όζω*= to smell) is an unstable gas made up of 3 oxygen atoms. Therapy with a mixture of oxygen and ozone has various pharmacological effects. It has an anti-inflammatory action by reducing the synthesis of prostaglandins, a pain-relieving effect (improving tissue trophism and promoting its repair) and a relaxing effect on the muscles by increasing the amount of oxygen [54,55]. The systemic administration of a mixture of oxygen and ozone is specifically indicated for chronic inflammatory diseases, characterized by a high oxidative stress secondary to an excess of ROS [56]. As we have already seen, endometriosis is a disorder associated with inflammation and oxidative stress and it has been postulated that intraperitoneal ozone treatment can protect antioxidant systems and down-regulate the concentration of inflammatory substances in the context of peritoneal implants. In a study conducted on rats, ozone therapy was shown to significantly reduce the

volume of peritoneal endometrial implants, with minimal adverse effects on the ovarian tissue [57]. *Aktun, et al*. [58] studied the potential therapeutic efficacy of ozone therapy in the treatment of induced peritoneal endometriosis in rats by comparing its activity with a GnRH agonist (leuporide acetate) and placebo. After ozone therapy, a significant increase in the activity of antioxidant enzymes, Such As Superoxide Dismutase (SOD) and a reduction in oxidative stress markers such as Malondialdehyde (MDA) were found in the peritoneal fluid.

According to the authors, repeated administration of ozone-oxygen therapy in non-toxic doses inhibits the growth of endometrial implants. Furthermore, no alterations in the serum levels of AMH were highlighted even if the number of primordial and preantral follicles had decreased after ozone therapy. However, the number of atretic follicles was similar in ozone therapy than in the control groups. Finally, we must also remember the important direct effect of ozone on antioxidant substances when it is administered by insufflation into a cavity, whether intraperitoneal or intrauterine. In conclusion, the anti-inflammatory action of ozone therapy could play an important role in the treatment of endometriotic implants through its endogenous antioxidant mechanism and be of great relief for women suffering from endometriosis.

Immunotherapy

There is a significantly higher incidence of immune-related disorders in patients with endometriosis, particularly referring to autoimmune diseases, or their genetic predisposition, and celiac disease. The coexistence of endometriosis with systemic lupus, Sjögren's syndrome, rheumatoid arthritis, autoimmune thyroiditis, multiple sclerosis, Addison's disease and Chron's disease has been shown to be much higher than in women without autoimmune diseases. Although there are no convincing data on a possible causal mechanism linking these pathologies with endometriosis, it is hypothesized that impaired immune regulation is the substrate that associates endometriosis with autoimmune diseases [59]. Furthermore, concomitant autoimmunity is associated with a more severe course of endometriosis [60]. Recently, some studies have hypothesized a potential link between endometriosis and celiac disease, as these conditions share some similarities [61,62] and patients with endometriosis have been found to suffer from celiac disease three times more often than healthy women. In fact, the results of *Santoro, et al*. [63], who confirm the potential association between celiac disease and endometriosis in Italian women, state that this trend does not reach statistical significance, however suggesting to implement screening for celiac disease in women with endometriosis. Certainly, however, the gluten free diet can eliminate the pro-inflammatory stimulation [61] related to the strong immune background present in endometriosis. Radoslaw and Coll postulate that immunotherapy may be a promising and useful approach in the treatment of these conditions [64].

The Fitness

Activity and exercise may have a number of beneficial effects on the symptoms associated with endometriosis. Merete Tennfjord and Coll. [65] evaluated eleven databases with eligibility criteria for women with established endometriosis receiving a physical activity protocol with standardized exercises. The Authors confirmed that, unfortunately, efficacy data cannot be reliably determined based on the existing literature. However, the potentially beneficial role of activity and physical exercise should be communicated to women with symptoms associated with endometriosis, considering that it is necessary to focus on the type and dose of physical activity. The study by Ensari [66] also provides evidence that regular physical exercise is a potential pain moderator, provided that one exercises at least 3 times a week. Unfortunately, specific recommendations for the management of endometriosis pain are almost completely absent and therefore it is necessary to organize future studies that can serve to investigate the effects of physical activity on endometriosis pain with a focus on various types of exercises, their intensity and duration and structure adequate guidelines. Since patients with endometriosis can show complex symptoms, the cooperation of multiple specialists, such as physiotherapists and osteopaths together with gynecologists, could improve the quality of clinical research in this field and obtain favorable results on the symptoms and evolution of the disease.

Osteopathy

Women suffering from endometriosis live with a constant pelvic contracture, which is partly due to the disease and

partly linked to central inflammation phenomena that activate the mechanism of chronic pain. The memory of pain is almost always present and this leads the patient to remain in a sort of lasting defensive structural attitude. Osteopathic interventions can be used as complementary strategies to better manage the different conditions of endometriotic disease. 60% of women diagnosed with endometriosis report chronic pelvic pain and it has been observed [67] that these patients are 13 times more likely to experience abdominal pain than healthy subjects. *Jaiswal et al.* [68] found a high presence of cytokines and growth factors in peritoneal fluid samples taken from women with endometriosis, which could contribute to the pathogenesis of pain and be considered real diagnostic markers. Indeed, in 20-28% of patients operated on for deep infiltrating endometriosis, a recurrence of symptoms is reported even in the post-surgical phase, despite the absence of new foci [69]. This evidence has led some researchers [70] to explore neuropathological aspects inherent in neuroplastic modification patterns typical of chronic pain (central-periphery bidirectional communication, resting state functional connectivity) and to investigate topics such as inflammation, including neurogenic inflammation, neuro angiogenesis, peripheral and central sensitization, allodynia and hyperalgesia [71].

Magdalena and Coll. [70] found that in women with chronic pelvic pain there is an increased connection at rest between the areas belonging to somato-sensory pain processing and the regions responsible for cognitive and emotional processing. Through a cross-sectional study and insight into the relationships between myofascial dysfunction, sensitization and chronic pelvic pain, *Phan et, al.* [72] have added a piece to the manual therapeutic approach for endometriosis. Indeed, in affected women, an emerging semiotic finding is the reproducibility of symptoms by palpation of the soft tissues of the pelvis. These findings seem to suggest that in these women the parameters of myofascial sensitization and dysfunction extend beyond the pelvic region in relation to the modification of the central functional connection.

It would therefore be legitimate to hypothesize that muscle spasms localized in the soft tissues of the pelvic floor, through precise mechanisms of viscero-somatic convergence, may act as triggering factors and perpetuation of sensitization. Manual therapies therefore seem to prove to be a possible approach that can be integrated with common endometriosis intervention strategies. In addition to the molecular component, which we have just analyzed, the cellular component present in peritoneal fluids also seems to play an important role in the genesis of endometriosis, such as T lymphocytes, which secrete lymphokines, and macrophages related to MIF (macrophage migration inhibitory factor). In recent years [73], there has been an increased interest in approaches focused on the lymphatic system whose stomata have been identified in various areas of the peritoneum. These contain macrophage-rich lymphatic aggregates that can engulf particles and pathogens present in the peritoneal cavity and are involved in the resolution of peritoneal inflammation and infection [74]. Even respiration seems to be one of the factors that can most influence subdiaphragmatic lymphatic absorption which drains fluids from the peritoneal cavity towards the vascular system [75]. During exhalation, the diaphragmatic muscles relax and, by separating, induce a valve opening such as to allow lymphatic access to the stomata. Finally, coherently with the concepts of bodily integrity and totality, it is appropriate to report the considerations of *B. Bordoni* [76]. The author invites us not to forget the phenomena of functional synergy of the pelvic diaphragm with the rest of the body diaphragms: buccal, upper thoracic, thoracic proper, pelvic. A correct balance of the aforementioned anatomical structures could in fact guarantee an important beneficial action on the circulation of body fluids (e.g. blood and lymph) and on the general health of the individual. The treatment of the five diaphragms is essential because preparing the body by releasing the diaphragmatic muscle-tendon structures makes the work on visceral efficacy more effective. Both manual therapies and the action on the lymphatic drainage of the peritoneal cavity, influenced by breathing, could make an additional contribution to new osteopathic intervention rationales for the treatment of endometriosis.

Acupuncture

Traditional Chinese Medicine (TCM) does not consider endometriosis as a disease in its own right, but recognizes, treats and characterizes the signs and symptoms associated with it. There is no univocal diagnosis of endometriosis but a set of various pictures capable of determining the

symptomatology accused by the patient. According to the Chinese view, the fundamental mechanism underlying this pathology is blood stasis, which can be constitutional, derive from various types of disorders, from emotional factors, from an incorrect diet, from a bad lifestyle or more often by a combination of several factors. According to TCM, the woman is Yin compared to the man and this not only for elements concerning the general physical conformation, but above all because she uses a lot of blood, liquids and fluids in general and is in the continuous need to regenerate them. Blood, generated by the organs, is the basis of the menstrual mechanism, but the Qi that moves it and gives it dynamism is almost inseparable from it. In TCM Qi is considered as the driving force of organ functions ("Kidney Qi", "Liver Qi", etc.), and at the same time, it is considered what nourishes and sustains all body tissues. Also, in TCM, Qi is often treated almost like a bodily fluid.

Blood and Qi, although distinct, are inextricably linked by relationships of mutual dependence: "Qi moves and keeps the Blood in the vessels, it is the commander of the Blood". Blood nourishes the organs which then produce and regulate Qi, <<Blood is the mother of Qi>>. A regular flow of Blood is a necessary condition for the regularity of Qi, but in the same way, a regular diffusion of Qi is an indispensable condition for the diffusion of Blood. To further underline this relationship, traditional medicine states that << Blood and Qi are two names for the same nature >>. Menstrual flows, fertility, pregnancy, lactation and all the physiological balance of the female organism are related to Qi, Blood, Jin and Tian gui. These substances are intimately connected to each other: the Qi governs the Blood and the Blood produces the Qi, the Jin nourishes the blood and the Blood in turn generates the Jin, the Jin of the Kidney generates the Qi of Kidney, the state of the Kidney is closely related to the Tian gui. "Tian Gui is the feminine Essence" even if it is also present in the male. Tain Gui is directly related to the kidney and is closely integrated and similar to the modern biomedical urinary and endocrine system. The Tian Gui is associated with the material basis of the male and female reproductive systems [77]. In the balance of the female genital system, the organs connected to the Yin and the Blood are naturally of particular importance and therefore the Liver, the Kidney, the Spleen (the three Yin of the foot). The greater involvement of one or the other will be suggested by the complained symptomatology.

The Kidney governs the uterus through the ancestral Qi, yanqi which is located there, and contains the Tiangui, which allows the menstrual cycle and fertility. This occurs through the lower Jiao and the Ren mai, Chong mai and kidney meridians. The Spleen, the trophic organ par excellence, nourishes the ovary, also conserves the Blood and therefore presides over the physiology of the menstrual cycle; this occurs via the middle Jiao and the Stomach and Spleen meridians. The Liver <<preserves the Blood>>, that is, it stores it, just as the kidneys are the repository of the Jin, the Liver is the repository of the Blood. The Blood storage function is not static, but is carried out dynamically through a continuous release and collection action, regulating its distribution throughout the body and it is a part of this Blood which, having descended into the Ren mai and Chon mai meridians, becomes menstrual: in reality for traditional Chinese medicine, the Blood, having reached the uterus through these meridians, is made available for the formation of the fetus and only if this does not happen, having become "old", is it expelled outside with menstruation after a month . All the work related to the movement of the Blood towards these compartments and the new storage that preludes the next cycle is regulated by the Liver: as a result, only a well-harmonized Liver can guarantee menstrual periodicity and regularity. Finally, the course of the Liver meridian underlines the important correlations it contracts with the physiology of the female genital and reproductive system: the meridian surrounds the genitals, crosses the pelvis and reaches the breast. The meridians, related internally with the Organs, connect the whole organism in an organic whole and perform the function of transporting Qi and Blood and regulating Yin and Yang. Female physiology is practically linked to the curious meridians Chong mai, Ren mai, Du mai and Dai mai (the curious meridians are virtual meridians that appear when there are energy disturbances in the Main Meridians by acting as energy reserves) which, in addition to carrying the 'Congenital, ancestral vital energy, in the whole body and in the curious viscera (including the uterus), integrate the functions of the main meridians [78].

Therefore, in endometriosis, according to Traditional Chinese Medicine, Qi stasis dysmenorrhea occurs with blood stagnation, described as abdominal pain that precedes the menstrual cycle by one to two days or is associated with it in the first days of the flow, often the patient feels a sense

of tension in the lower abdominal quadrants, with difficulty initiating and expelling the menstrual cycle itself. The pain sometimes also affects the hypochondria, the hips, the chest, the sinuses (areas crossed by the meridians mentioned). Menstruation is scanty, dark sometimes with clots. What has been described leads to the selection of specific points on which the treatments are performed: from three to five main therapeutic points are used to which secondary points are added; the needles are positioned perpendicular to the skin plane with the application of moxibustion or infrared lamp. All the needles are kept in place for 20-30 minutes and manipulated manually or with a variable frequency and low intensity electrostimulator in order to warm up the meridians and disperse the cold, mobilize the blood and regulate menstruation. Treatments can be performed daily in the menstrual phase, and twice a week in other periods for cycles of 15 sessions followed by a monthly session [79]. Acupuncture associated with conventional treatments of endometriosis contributes to the decrease of dysmenorrhea and to a greater regularity of the menstrual cycle.

Psychological Support

Pain, which is the most important symptom of endometriosis, puts women in difficulty especially when it is intense or repetitive. Pain can affect at different levels: physical, social, emotional, relational, existential and above all it can force you to deeply review some life projects, such as motherhood. Intense pain can be perceived as an enemy to be fought at any cost. But in this way, since the seat of pain is the body, one runs the risk of transforming one's body into an enemy rather than an essential resource for a full life [80]. To proactively manage this condition, the "recognition" phase is essential: the frequent delay in diagnosis - often due to common symptoms (such as, for example, menstrual pain), or overlapping with other pathologies, can generate confusion, with a decrease of self-confidence, of one's ability to listen and understand one another, to evaluate one's state of well-being and malaise [81]. An important first step in working with women is to separate her profound identity from the disease, to allow her to build a realistic self-narration, trying to give a new meaning to her life experience, integrating the disease, thus ceasing to fight it as a bitter enemy, instead starting a process of acceptance [82]. This integration is also facilitated by the use of concrete tools that help manage everyday life: techniques such as meditation, guided visualization, also supported by Virtual Reality, help to relax body and mind to "stay" in time present, an important step to access well-being and serenity [80].

Furthermore, since they are methods that restore the central role of protagonist to the body, they also provide an opportunity to feel it as an ally and not as a "traitor" or "obstacle". These concrete tools can be learned and managed independently over time, to improve the quality of one's life. Thoughts characterized by hopes, realistic and positive opportunities, have a beneficial effect on the emotional state of the person, which in turn affects the neurological state and the immune system, as now amply demonstrated by PNEI (Psyco Neuro Endocrine Immunology). The activation of this virtuous circle (body-thoughts-emotions) has beneficial effects on the psychophysical health of women, and consequently also on the network of relationships that surround them [83]. Indeed, it is important to provide support to people who share the life of women with endometriosis [83]. The couple may have to review their approach to sexuality, or objectives and ways of thinking about forms of parenting outside of the biological one, in order to accept a daily life marked by the manifestations of the disease. The partner, in particular, could find himself having to review his own way of being at the side of his partner, accepting the fact that he cannot do anything concrete to change the situation, but instead accompanying the process of acceptance, rather recognizing the value of "being there" [84].

Note: PNEI is a new model of personal care that deals with the mutual interaction between behavior, mental activity, the nervous system, the endocrine system and the immune response of human beings.

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Conclusions

In consideration of the fact that the medical and surgical therapy of endometriosis have sometimes important limits of use, it is often necessary to address the disease "as a whole" by considering other forms of treatment. Endometriosis is a complex pathology, which can affect a woman's life on several levels, sometimes in a devastating way, and which therefore needs to be taken care of globally in order to be

integrated and accepted into a full and conscious life plan, allowing those who experience it, at different levels, to manage it without necessarily being crushed by it.

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Conflict of Interest

No conflict of interest.

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