Natural Approaches to Relieving Endometriosis

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Endometriosis is a common gynecologic condition in which endometrial tissue grows in ectopic locations. It is estimated that 5 million women of reproductive age, or 10 percent of women, in the United States, are affected by this disease.[1] Approximately 20 percent of women with chronic pelvic pain and 30–45 percent of women with infertility have endometriosis.[2]

Endometrial tissue outside the uterus responds to normal hormonal signaling from estrogen and progesterone. Just as in the uterus, these hormones cause cyclic growth and bleeding of the tissues, often into the peritoneal cavity. Adhesions and inflammation also develop from the accumulation of tissue.

The etiology of endometriosis is still unknown and no current theory explains all the aspects of the disease. However, increasing evidence suggests that environmental estrogenic toxins and the immune dysfunction they cause may be implicated in the etiology and progression of the disease.

Etiology

Researchers have found a genetic correlation in endometriosis development. Women who have first-degree relatives with the disease have ten times the risk of developing endometriosis.[3] In addition, women with family histories of endometriosis are statistically more likely to experience an earlier onset and increased severity of the disease.[4]

Recent studies suggest environmental toxin exposure and immune dysfunction as possible factors in the onset and progression of endometriosis. Chlorinated hydrocarbons such as dioxin and polychlorinated biphenyls (PCBs), which have adverse clinical effects on the immune and endocrine systems, have been associated with endometriosis. For example, several studies on monkeys have demonstrated a direct correlation between dioxin exposure and endometriosis. In these studies, the amount of dioxin exposure was correlated with severity of disease. The monkeys showed immune system dysfunction similar to the immune abnormalities seen in women with endometriosis.[5,6]

Studies have also shown that dioxin modulates steroid receptor expression, (thus changing hormonal responses), decreases natural-killer (NK) cell activity, inhibits T-lymphocytes, and stimulates macrophages in the peritoneal fluid, thus affecting angiogenesis and concentration of cytokines and growth factors.[7–9] Dioxins and PCBs suppress the immune system; impair reproductive capabilities; increase the risk of multiple cancers, diabetes, and cardiovascular disease; and reduce memory function. Exposure to dioxin and dioxin-like PCBs occurs primarily via food and pesticides.[10–14]

Other risk factors have been implicated in endometriosis, such as menstrual cycles that are less than 28 days, heavy flows lasting 5 or more days, menses that last more than 7 days, and increased estrogen levels. Endometriosis development is also associated with increased body fat, a high-fat diet, lack of exercise, and use of intrauterine devices.[15] In a small study, researchers found a significant association between natural red hair color and frequency of the disease.[16]

Symptoms

Classically, patients with endometriosis present with chronic or cyclic pelvic pain and infertility. Pain often begins 1–2 days prior to onset of menstruation and may last several days or throughout the menstrual period. Additional symptoms may include dyspareunia, abnormal uterine bleeding, cyclic pain with defecation or urination, blood in urine or stool, constipation, diarrhea, nausea, vomiting, and fainting. However, one third of women diagnosed with endometriosis are asymptomatic. The severity of pelvic pain does not correlate with the extent of the disease though it may correlate with the proximity of adhesions to nerve endings (see box entitled Symptoms of Endometriosis).[17]

Pathology

Endometriomas are commonly found on the ovaries; fallopian tubes; peritoneal lining; cervix; colon; appendix; vagina; and uterosacral, broad, and round ligaments. In severe cases, adhesions are also found on the bladder, kidney, vulva, arms, legs, lungs, nasal mucosa, spinal column, and sites of previous surgical incisions.[2] Two thirds of women with endometriosis have their ovaries affected; in 30 percent of women local lymph nodes are involved; and in 10–15 percent of women, the sigmoid colon is affected.[2]

The immune system is implicated in the development, progression, and symptoms of endometriosis. Both humoral and cell-mediated acquired immune responses are abnormal in women who have the disease. Humoral immune responses are mediated

Symptoms of Endometriosis

- Chronic pelvic pain
- Infertility
- Dyspareunia
- Abnormal uterine bleeding
- Cyclic pain with defecation or urination
- Blood in urine or stool
- Constipation, diarrhea
- Nausea, vomiting
- Fainting

Procedures for Diagnosing Endometriosis

- Physical examination
- Ultrasound or magnetic resonance imaging
- Laparoscopy or laparotomy
- Serum CA-125 testing

by immunoglobulins or antibodies such as immunoglobulin E (IgE), IgG, IgD, IgA, and IgM. T-lymphocytes mediate the cellular immune responses and have receptors on their membranes, which respond to antigens. Antigens binding to these receptors activate the cells to release a number of cytokines, which cause inflammation and tissue damage. Studies have shown that many of these proinflammatory chemical mediators are elevated in the peritonea of women with endometriosis.[18]

Women with endometriosis have abnormalities in immune-functioning cells such as NK cells, cytotoxic T-cells, B-lymphocytes, macrophages, and monocytes.[19] NK cells are responsible for destroying endometrial cells and are decreased in function and concentration in women with endometriosis.[18,20]

Studies have also shown that, in affected women, cytotoxic T-cells are decreased and T-suppressor cells are increased. T-suppressor cells reduce the immune response to foreign or host agents; the increase in these cells may reduce the ability of the immune system to identify and remove the ectopic endometrial tissue.[21] The macrophage count has been shown to be elevated in the peritoneal fluid in women with endometriosis.

Macrophages secrete cellular mediators, such as prostaglandins, fibronectins, integrins, and other cytokines that promote the development and progression of endometriosis. In women with endometriosis, the macrophages do not appear to phagocytize. Failure of the macrophages to phagocytize may explain the persistence of ectopic endometrial tissue in the peritoneal cavity.[22]

Other studies have shown that macrophages secrete high levels of the cytokine transforming growth factor–β (TGF-β) that inhibits NK cells while increasing scarring and fibrosis. TGF-β also stimulates angiogenesis, which allows the ectopic endometrial tissue to generate its own blood supply.[23] Proinflammatory cytokines, such as tumor necrosis factor–α (TNF-α), interleukin-1 (IL-1), and IL-6, are also elevated in the peritoneal fluid of women with endometriosis.[18]

Researchers have shown that B-lymphocyte antibody production is abnormal in women with endometriosis, who have increased levels of IgG and IgM antibodies. In addition, autoantibodies against the ectopic endometrium are found in the cervical and vaginal secretions and sera in these women.[24,25] Researchers have linked endometriosis to such diseases as systemic lupus erythematosus, rheumatoid arthritis, multiple sclerosis, and Sjögren's syndrome, which suggests that endometriosis may have an autoimmune component. Other conditions, such as fibromyalgia, chronic fatigue syndrome, hypothyroidism, allergies, asthma, and eczema, are significantly more common in women with endometriosis than in the general female population of the United States.[26] Endometriosis is also correlated with an increased risk of ovarian cancer and non-Hodgkin's lymphoma.[27,28]

Diagnosis

Diagnosis of endometriosis is often difficult because the disease has various presentations. Physical examination of a patient may reveal a fixed retroverted uterus, enlarged ovaries, and nodules on the uterosacral ligaments. Transvaginal sonography is often utilized to access large ovarian, intestinal, or bladder endometriomas. It is less accurate for rectovaginal, vaginal, or uterosacral lesions. CA-125 is a blood test that can indicate the presence of endometriosis, although the test is not utilized often for diagnostic purposes because of its low sensitivity. Laparoscopy with biopsy provides a definitive diagnosis (see box entitled Procedures for Diagnosing Endometriosis).

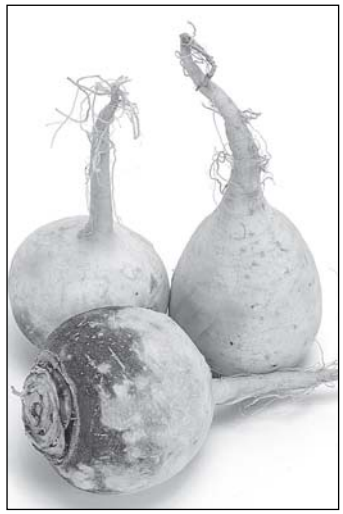
Conventional Treatment

Conventional medical treatment focuses on reducing estrogen stimulation, managing pain, and preserving fertility. At the time of laparoscopic diagnosis, treatment often begins as visible lesions are removed or destroyed. Hormone therapy is commonly utilized because endometrial tissue responds to hormone stimulation. Estrogen has been shown to increase aberrant endometrial lesions, while progesterone and androgens may decrease implant size. Hormone modulation does not cure endometriosis and the disease often returns upon discontinuation of pharmaceutical therapy.[2]

Pharmacology

Nonsteroidal anti-inflammatory drugs (NSAIDS) are commonly prescribed to manage pelvic pain. Prostaglandins are responsible for much of the pain associated with endometriosis; because NSAIDs inhibit prostaglandin synthesis, they often relieve pain.

Hormones typically used in treatment are danazol, a weak androgen that decreases follicle-stimulating hormone (FSH) and luteinizing hormone (LH) secreted from the pituitary gland, thereby inhibiting ovulation and menstruation; oral contraceptives; progestins; and gonadotropin-releasing hormone agonists (GnRH agonists) that suppress FSH and LH and inhibit ovulation. Studies have demonstrated reduction of symptoms in 67 percent or more individuals on oral contraceptive treatment (see box entitled Pharmacologic Interventions for Treating Endometriosis).[29]



Clockwise from top: walnuts, sunflower, turnips, and corn.

Nutrient and Herbal Interventions

Fatty-Acid Supplements

Supplementation with eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), alpha-linolenic acid (ALA), and gamma-linolenic acid (GLA) can reduce inflammation. The omega-3 fatty acids EPA and DHA compete with arachidonic acid (AA) in the lipo– and cyclo-oxygenase pathways and therefore decrease levels of inflammatory eicosanoids.[30–32] Studies have demonstrated that fish oils high in DHA and EPA reduce the production of proinflammatory cytokines, such as IL-1, IL-2, and TNF. These fish oils also can suppress B- and T-lymphocyte synthesis and decrease antibody production.[33–36]

GLA, an omega-6 fatty acid found in borage (*Borago officinalis*) seed oil, evening primrose (*Oenothera biennis*) oil, and black currant (*Ribes nigrum*) oil, is metabolized in the body to the anti-inflammatory series 1 prostaglandins and inhibits AA from forming proinflammatory leukotrienes.[37] Linoleic acid (LA) is an omega-6 fatty acid that is the precursor to GLA and can be used to stimulate the anti-inflammatory pathway. LA is commonly found in the oils of corn, safflowers, sesame, soybeans, sunflowers, walnuts, grape seeds, and wheat germ.

ALA is an omega-3 fatty acid found in flax *(Linum usitatissimum)*, rapeseed (*Brassica napus*), and soy (*Glycine soja*) beans as well as in walnuts, pumpkin seeds, and perilla seeds and is a precursor to EPA. The enzyme delta-6-desaturase converts LA and ALA to GLA and EPA and requires magnesium, vitamin B_6, and zinc as cofactors. Often, clinical failure of essential fatty acid (EFA) intervention results from the inadequate presence of these cofactors.

Vitamin E

Lipoxygenase catalyzes the conversion of AA to leukotrienes, which are potent inflammatory mediators. Vitamin E alters the leukotriene pathway by inhibiting proinflammatory prostaglandin E2 and leukotriene B4 formation. γ-Tocopherol, the most common form of vitamin E in American diets, decreases TNF-α, which is elevated in women with endometriosis.[38] Studies also indicate that vitamin E succinate and vitamin A protect tissues against damage from dioxin exposure.[39,40] It is important to keep in mind, however, that high-dose vitamin E therapy has a significant antiplatelet aggregating effect, which thins the blood and increases the likelihood of hemorrhage, independently or in conjunction with anticoagulant and antithrombotic pharmaceutical drugs.[40]

Pharmacologic Interventions for Treating Endometriosis

- Nonsteroidal anti-inflammatory drugs
- Danazol
- Oral contraceptives
- Progestins
- Gonadotropin-releasing hormone agonists

Vitamin C

Vitamin C increases T-lymphocyte activity, phagocyte function, leukocyte mobility, and interferon and antibody production. Studies have shown abnormal phagocytes, antibodies, and cytokines in women with endometriosis, so vitamin C may be

Natural Interventions for Endometriosis

Interventions	Doses
Eicosapentaenoic acid	1–3 g per day
Docosahexaenoic acid	1–3 g per day
Alpha-linolenic acid	1.2–2 g per day
Gamma-linolenic acid	900–1500 mg per day
Vitamin E (mixed tocopherols)	400–800 IU per day
Vitamin C	1–3 g per day
Beta carotene	25,000–50,000 IU per day
Milk thistle (*Silybum marianum*)	420 mg, per day, standardized to 70–80 percent silymarin
Crampbark (*Viburnum opulus*); black haw (*Viburnum prunifolium*)	5–10 mL, 3 times per day
Black cohosh (*Cimicifuga racemosa*)	40–80 mg, 2 times per day, pro viding 4–8 mg triterpene glycosides
Natural progesterone	1/8 to 1/4 teaspoons topically, 2 times per day, on days 15–28 of the menstrual cycle

IU = international units.

therapeutically useful. Because it is an antioxidant, vitamin C can protect cells from reactive oxygen species known to cause tissue damage and disease. This protective effect may also prevent tissue damage from dioxin and PCBs. Women with high estrogen levels, oral contraceptive users, and nicotine users will have increased vitamin C excretion and measurably lower plasma levels, and these women might require higher levels of supplementation.[41,42]

Beta-Carotene

Beta-carotene has been shown to prevent lipid peroxidation and reduce free-radical DNA damage.[43,44] Beta-carotene can also increase the function of NK cells.[45] Carotenoids provide approximately 50 percent of the vitamin A in the American diet, and studies have shown that vitamin A has protective effects against dioxin-induced tissue damage.[42,46]

Milk Thistle

Silymarin, the main active constituent in milk thistle (*Silybum marianum*), has been shown to reduce TNF cytotoxic and proinflammatory functions.[47] Constituents of milk thistle inhibit lipid peroxidation and are antioxidants and free-radical scavengers.[48] Silymarin also prevents toxin penetration into liver cells and may be able to decrease toxic metabolite formation in the liver. In addition, estrogen clearance may be increased as a result of silymarin inhibition of β-glucuronidase.[49]

Crampbark and Black Haw

Crampbark (*Viburnum opulus*) and black haw (*Viburnum prunifolium*) are antispasmodics. Scopoletin and viopudial are two constituents that, because of their antispasmodic action on smooth muscle, can decrease menstrual cramps and other muscle spasms. In addition, the scopoletin in black haw has been shown to relax the uterus.[50] Animal studies have shown that viopudial in crampbark has cholinergic activity that can decrease blood pressure, heart rate, and myocardial contractility.[51]

Black Cohosh

Constituents of black cohosh (*Cimicifuga racemosa*) are anti-inflammatory and have estrogen-like activity.[52,53] Animal studies suggest that black cohosh suppresses pituitary secretion of LH. Studies indicate that the herb may be a selective estrogen receptor–modulator that has estrogenic effects on some tissues and antiestrogenic effects on other tissues.[54] New data suggest that black cohosh does not bind estrogen receptors, stimulate the growth of estrogen-dependent tumors, or upregulate estrogen-dependent genes.[55]

Natural Progesterone

Progesterone is commonly prescribed to treat menopausal symptoms, abnormal uterine bleeding, premenstrual syndrome, endometrial hyperplasia, and infertility. Progesterone causes uterine smooth-muscle relaxation.[56] Low levels of progesterone can cause a relative estrogen excess; excessive estrogen is implicated in endometriosis. Thus, a clinical trial of progesterone therapy in conjunction with immunologic and inflammatory modulation of the internal biochemical milieu appears to be a rational approach to treating endometriosis.

Dietary Interventions

A well-nurtured body is a more resilient one. A healthy diet and stress reduction can help alleviate not only the symptoms but also the imbalances that underlie endometriosis. Diets high in fruits and vegetables provide the vitamins and flavonoids required to decrease inflammation and oxidation. Nutritional status affects the immune response, inflammation, and hormone regulation.

Studies have demonstrated that dietary vitamins and minerals protect patients against immune suppression caused by dioxin exposure and that dietary fiber promotes fecal excretion of dioxin.[57] The phytochemical indole-3-carbinol found in cruciferous vegetables such as kale, turnips, broccoli, cauliflower, cabbage, collard greens, and mustard greens, may prove to be clinically useful for treating endometriosis because this phytochemical modulates estrogen levels. Liver function can be improved by increasing intake of artichokes, burdock root, beets, dandelion greens, lemons, carrots, onions, and garlic.

Diets high in EFAs and low in animal products decrease AA and thus inflammatory mediators. GLA is found in black current seed, borage oil, and evening primrose oils. EPA and DHA are found in fatty fish including herring, salmon, cod, mackerel, sardines, trout, and kipper. Studies suggest a correlation between endometriosis and caffeine consumption; caffeine should therefore be strictly avoided.[58] In addition, alcohol should be limited because of its potential estrogenic effects and depletion of B vitamins.

Conclusions

Endometriosis can be treated with a variety of herbs, supplements, and dietary interventions, thus reducing or eliminating the need for conventional pharmaceutical treatments. As with any intervention, the approach to each patient needs to be individualized, taking into account each patient's body chemistry and needs. □

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