

## Endometriosis

Endometriosis is caused by the growth of endometrial tissue outside the uterus. These collections of endometrial tissue cause lower abdominal pain and may cause infertility and gastrointestinal complications. Approximately 5 million American women, mostly between the ages of 25 and 44, suffer from endometriosis, and the disease affects about 30 to 45 percent of women with infertility (Herbst A et al 1997).

The cause of endometriosis is unknown. According to the most prevalent theory, endometrial tissue refluxes into the abdominal cavity, where it becomes established. An established colony of endometrial tissue continues to act like normal endometrial tissue even though it is outside the uterus. The tissue responds to the normal hormonal fluctuations in a woman's monthly cycle. During the first part of the cycle, the tissue colony thickens and grows in response to estrogen. In the latter part of the cycle, the tissue degenerates and bleeds, sloughing off the excess cells, causing inflammation and damage to adjacent tissue.

Women with endometriosis have elevated levels of inflammatory chemicals, providing a therapeutic target for anti-inflammatory dietary supplements. In addition, Life Extension has identified novel approaches to nutritional estrogen modulation that may help reduce the severity of the disease and the risk of hormone-dependent cancers, including breast and ovarian cancer.

In about two-thirds of cases, the ovaries are colonized by endometrial tissue. Other common sites for tissue to implant include the fallopian tubes, the lining of the pelvic cavity, uterine ligaments, and the outside lining of the uterus, cervix, colon, appendix, and vagina. In severe cases, adhesions of endometrial tissue are found on the vulva, bladder, kidney, arms, legs, lungs, nasal mucosa, spinal column, and sites of previous surgical incisions (Herbst A et al 1997).

While endometrial reflux is the most common theory, it does not fully explain the disease. At least some degree of menstrual reflux occurs in 75 to 90 percent of women, yet the rate of endometriosis is much lower. Obviously, an additional mechanism must be at work.

One theory that might help explain why some women suffer from endometriosis is the autoimmune theory. According to this theory, macrophages, which would normally be expected to destroy the endometrial cells, actually contribute to their colonization. In addition, numbers of T cells and natural killer cells, which are also elements of the immune system, are reduced. There is also evidence that the misplaced endometrial cells are resistant to removal by immune cells.

The autoimmune theory of endometriosis is supported by the frequent finding of autoantibodies in women with endometriosis and by the high rate of other autoimmune conditions among women with endometriosis, including rheumatoid arthritis, multiple sclerosis, and systemic lupus erythematosus (Sinaii N et al 2002). Women who have had recurrent immune-mediated miscarriages may be prone to endometriosis (Ulukus M et al 2005).

Genetics factor into the development of endometriosis. Women with a first-degree relative who has endometriosis have a tenfold increased risk of developing the disease (American College of Obstetricians and Gynecologists 1993). Also, women with a family history of endometriosis are more likely to have earlier onset and increased disease severity than women without a family history (Dmowski WP et al 1997).

### HOW ENVIRONMENTAL TOXINS MAY CAUSE ENDOMETRIOSIS

An association between endometriosis and exposure to chlorinated hydrocarbons, such as polychlorinated biphenols (PCBs) and dioxin, has been demonstrated in laboratory animals (Rier SE et al 1995; Mayani A et al 1997); some human data support the association. These toxic chemicals can affect hormones and disrupt immune function.

Dioxin has been shown to alter hormonal responses and immune system function (Clark GC et al 1991; Neubert R et al 1991; Koninckx PR 1999; Safe S et al 1991). One study showed a direct link between exposure to dioxin and the incidence of endometriosis in monkeys. Severity of disease was directly correlated with the dose of dioxin. Monkeys in the study showed abnormalities in their immune systems similar to the changes seen in women with endometriosis (Rier SE et al 1993, 2001).

Human exposure to dioxin and dioxin-like PCBs is primarily through food and pesticides. Dioxin and dioxin-like PCBs have been shown to increase the risk of multiple cancers, diabetes, and cardiovascular disease; impair prostate development and reproductive capabilities; reduce memory function; and suppress the immune system (Roman BL et al 1998; Michalek JE et al 1999; Barrett DH et al 2001; Crump KS et al 2002; Lind PM et al 2004).

## DIAGNOSIS AND CONVENTIONAL TREATMENT OPTIONS

The many presentations of endometriosis often make diagnosis difficult. The most common symptoms of endometriosis are abnormal pelvic pain and pain during intercourse. Abnormal pelvic pain often begins one to two days before menstruation and may last for days or throughout the menstrual flow. Other possible symptoms include abnormal vaginal bleeding, constipation, diarrhea, frequent urination, and blood in the urine or stool. Nausea, vomiting, and fainting spells may also be present. The severity of symptoms does not correlate with the extent of the disease. Symptom severity has been proposed to correlate with the depth and location of adhesions in proximity to nerve endings (Lauersen N et al 1998).

In about a third of cases, however, endometriosis has no symptoms. In this instance, women are often diagnosed during a workup for infertility.

During a pelvic examination, doctors may identify findings characteristic of women with endometriosis. A retroverted uterus (a uterus that tilts toward the back rather than the front) may make endometriosis more likely, and tenderness during the examination, in the absence of findings that suggest infection, may also raise suspicion. Doctors may be able to feel nodules along various parts of a woman's internal anatomy that correspond to collections of endometrial tissue.

Definitive diagnosis of endometriosis requires a biopsy during explorative surgery. Surgical procedures such as laparoscopy involve a scope that is inserted through a small incision in the umbilicus (navel). The scope is used to visualize and biopsy tissue. Often ectopic tissue (tissue that is in the wrong place) is removed or destroyed at the time of the procedure. Laparotomy is a more invasive surgical procedure, usually reserved for women with extensive disease (Berek J 1996).

Less-direct diagnostic techniques include measuring levels of cancer antigen 125 (CA-125) and imaging.

**Imaging.** Although laparoscopy and surgery remain the gold-standard diagnostic tools, some less-invasive techniques can be helpful in establishing the diagnosis of endometriosis. Unfortunately, these techniques, such as magnetic resonance imaging and ultrasound, are likely to miss many smaller or less-active lesions. Transvaginal ultrasound (an ultrasound scan done with a probe placed in the vagina) can efficiently detect lesions larger than roughly three quarters of an inch in diameter (Brosens I et al 2004; Bazot M et al 2004).

**CA-125.** CA-125 is a protein made by certain cells in the body, including those of the uterine tubes, uterus, cervix, and the lining of the abdominal and chest cavities (peritoneum and pleura). CA-125 is elevated among women with endometriosis, and levels drop following surgery. However, CA-125 levels can also be elevated in a number of unrelated conditions, so it cannot be used reliably as a diagnostic or screening tool. It has value, however, in following the progression of the disease during or after treatment.

Conventional medical treatment focuses on pain management, reduction of estrogen stimulation, and preservation of fertility. Often treatment begins at diagnosis with laparoscopy, when visible lesions are removed or destroyed. The following medications may be used to treat endometriosis:

**Oral contraceptives.** Estrogen and progesterone combinations are commonly prescribed to manage endometriosis. Oral contraceptives are often prescribed continuously to help maintain endometrial tissue, preventing the eventual sloughing and bleeding that is associated with pain, as well as tissue damage and scarring. Studies have shown that 80 to 100 percent of women taking hormone-based therapies experience effective relief (Winkel CA et al 2001).

**Analgesics.** Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly prescribed to manage pelvic pain. NSAID treatment may be beneficial for mild pain relief but is often ineffective for severe symptoms. Side effects of NSAIDs include gastrointestinal pain and ulcers.

**Danazol.** Danazol is a synthetic form of testosterone used to thin the endometrial lining and reduce levels of estrogen. Danazol has been shown to have some immune-modulating effects as well. In one study, 89 percent of participants on danazol reported symptomatic improvement; 94 percent had improvement based on repeat laparoscopy or laparotomy (Barbieri RL et al 1982). Danazol's side effects include deepening of the voice and unwanted hair growth, in addition to sensitivity to sunlight.

**Progestins.** Progestins are synthetic progesterone derivatives prescribed when estrogen therapy is contraindicated or poorly tolerated. Progestins function similarly to other hormone therapies by inhibiting ovulation and menstruation. Ovulation often does not return promptly upon discontinuation of treatment.

**Gonadotrophin-releasing hormone agonists.** Gonadotrophin-releasing hormone agonists are used to induce a menopause-like state. Their long-term use will inhibit the release of luteinizing hormone and follicle-stimulating hormone from the pituitary, resulting in very low levels of estrogens and androgens, which will inhibit ovulation and menstruation. These drugs do not have the same effects on sex-hormone binding globulin as danazol and thus do not cause a rise in free testosterone, which translates into fewer

testosterone-related side effects.

Other drugs that have been studied for endometriosis include aromatase inhibitors (agents that interfere with estrogen and progesterone synthesis), selective estrogen receptor modulators (agents that prevent estrogen from binding to its receptors and exerting its full biological effect), and immunomodulators, including interferon.

## NUTRITIONAL AND SUPPLEMENT THERAPY

**Essential fatty acids.** Supplementation with essential fatty acids can reduce the inflammation associated with endometriosis by interfering with the production of prostaglandins or cytokines that mediate the pain and many other symptoms seen with endometriosis.

- *Docosahexaenoic acid and eicosapentaenoic acid.* Docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) are omega-3 long-chain polyunsaturated fatty acids found primarily in the oils of fatty fish such as salmon, mackerel, sardines, herring, trout, cod, kipper, pilchard, and menhaden. DHA and EPA compete with arachidonic acid in the production of prostaglandins, thereby reducing inflammation (Calder PC 2001; Connor WE 2001; Leaf A 2002). Fish oils also reduce the production of cytokines, such as interleukin-1, interleukin-2, and tumor necrosis factor (TNF), all of which are involved in producing and maintaining the inflammation associated with endometriosis. DHA and EPA have also been shown to down-regulate activity of immune system inflammatory cells and production of antibodies that are involved in the symptoms of endometriosis (French L 2005; Gazvani MR et al 2001; Yano Y 1992).
- *Gamma-linolenic acid.* Gamma-linolenic acid (GLA) is an omega-6 fatty acid found in borage seed oil, evening primrose oil, and black currant oil. GLA is metabolized in the body to series 1 prostaglandins, which decrease the inflammatory response and inhibit arachidonic acid from forming inflammatory leukotrienes (Leventhal LJ et al 1993). Precursors to GLA can also be taken to stimulate this anti-inflammatory biochemical pathway. Linoleic acid is an omega-6 fatty acid commonly found in corn, safflower, sesame, soybean, sunflower, walnut, and grape seed oils. Alpha-linolenic acid is an omega-3 fatty acid found in flax, canola, soybeans, walnuts, pumpkin seeds, and perilla seeds. The enzyme delta-6 desaturase converts linoleic acid and alpha-linolenic acid to GLA and requires magnesium, vitamin B6, and zinc as cofactors.

**Vitamin E.** Vitamin E is a fat-soluble vitamin that acts as a free-radical scavenger of lipids and fats. It protects cell membranes and prevents damage to membrane-associated enzymes. The most common form of vitamin E in American diets is gamma-tocopherol, which has been shown to decrease TNF-alpha (elevated in individuals with endometriosis) (FNB/IM 2000). Vitamin E succinate and vitamin A were found to reduce indicators of toxicity and damage in laboratory mice from dioxin exposure (Alsharif NZ et al 2004). In addition, one study suggested that women with endometriosis are under oxidative stress, which suggests a role for vitamin E as an antioxidant (Jackson LW et al 2005). Another lab study indicated that vitamin E inhibited endometrial cells (Foyouzi N et al 2004).

**Vitamin C.** Vitamin C (ascorbic acid) is found in many fruits and vegetables, especially citrus fruit. Vitamin C appears to increase T lymphocyte activity, phagocyte function, leukocyte mobility, and interferon and antibody production. As an antioxidant, ascorbic acid can protect cells from reactive oxygen species known to cause tissue damage and disease. Estrogen, oral contraceptives, and smoking (along with other forms of nicotine) increase vitamin C excretion, resulting in measurably lower plasma levels of vitamin C (Thorp VJ 1980; Lykkesfeldt J et al 2000).

**Beta-carotene.** Beta-carotene is a precursor to vitamin A. It is a carotenoid found readily in fruits, vegetables, grains, and oils. It has antioxidant activity, prevents lipid peroxidation, and may reduce free radical DNA damage (Omenn GS 1998; Manda K et al 2003). Beta-carotene and other carotenoids provide approximately 50 percent of the vitamin A needed in the American diet (Hickenbottom SJ et al 2002). Vitamin A has protective effects against damage from dioxin exposure, which has been implicated as a cause of endometriosis (Alsharif NZ et al 2004). In animal studies, beta-carotene has shown the ability to suppress the angiogenesis necessary for maintaining the growth of ectopic endometrial tissue (Tee MK et al 2006).

**Milk thistle.** Milk thistle (*Silybum marianum*) is a member of the Compositae family. Seeds are often used medicinally for liver disease. The main active constituent is silymarin, which has been shown to inhibit TNF (Manna SK et al 1999). Studies have found that TNF is elevated in women with endometriosis. Constituents of milk thistle have been demonstrated to provide antioxidant and free-radical-scavenging functions and to inhibit lipid peroxidation (Flora K et al 1998). Silymarin may increase estrogen clearance by means of its ability to inhibit the enzyme beta-glucuronidase (Agency for Healthcare Research and Quality 2000).

**Natural progesterone.** Natural progesterone is structurally identical to endogenous progesterone. It is synthesized from diosgenin, which is isolated from wild yam or soy and then converted to pregnenolone and progesterone in a laboratory. Progesterone has been shown to reduce inflammation in endometriosis and limit the growth of uterine tissue (Bulun SE et al 2006).

## NUTRITIONAL MODULATION OF ESTROGEN

One strategy that may be helpful with endometriosis is to modulate estrogen through nutritional means. Estrogen has many different metabolites, and research has shown that some metabolites are stronger and more dangerous than others. Certain

nutrients, such as indole-3-carbinol, may help increase weaker estrogens while decreasing stronger estrogens. Among patients with endometriosis, this finding may have two benefits. First, it would reduce the stimulatory effect of estrogen on the endometrial tissue, which may reduce the buildup of blood during the early part of the menstrual phase. Second, favorably altering the ratio of weaker to stronger estrogens may reduce the risk of breast and ovarian cancer.

Specifically, indole-3-carbinol has been documented to increase the ratio of weaker 2-hydroxyestrone to the stronger and carcinogenic 16-alpha hydroxyestrone (Reed GA et al 2005). It accomplishes this by encouraging synthesis of additional 2-hydroxyestrone (Yoshida M et al 2004).

A related natural approach to estrogen modulation may be found in a compound called diindolylmethane, a byproduct of indole-3-carbinol that has shown many cancer-fighting effects.

## ENDOMETRIOSIS AND OTHER DISEASES

Endometriosis has been associated with an increased risk of conditions associated with abnormal immune responses: systemic lupus erythematosus, rheumatoid arthritis, multiple sclerosis, and Sjögren's syndrome (Sinaii N et al 2002). Allergies, eczema, and asthma caused by a hypersensitivity reaction of the immune system are also increased in women with endometriosis. Fibromyalgia, chronic fatigue syndrome, and hypothyroidism are significantly more common in individuals with hypersensitivity reactions than in the general U.S. population (Sinaii N et al 2002).

A survey revealed that 42 percent of women with endometriosis have underactive thyroid glands (hypothyroidism). Women with endometriosis have a higher incidence of hypothyroidism than most women in the United States (Sinaii N et al 2002).

Endometriosis is also correlated with an increased risk of ovarian cancer and non-Hodgkin's lymphoma (Ness RB et al 2000; Olson JE et al 2002).

## LIFE EXTENSION FOUNDATION RECOMMENDATIONS

Endometriosis is one of the most common causes of pelvic pain in women. It is caused by growth of endometrial tissue in inappropriate places. Because endometrial tissue is sensitive to estrogen, which causes it to grow, women with endometriosis are discouraged from eating phytoestrogens, or plant-based estrogens, found in soy products. Phytoestrogens have been shown to encourage endometrial tissue growth (Edmunds KM et al 2005).

The following nutrients have been shown to reduce the inflammation associated with endometriosis and reduce endometrial tissue growth:

- **DHA and EPA**—at least 1400 milligrams (mg) EPA daily and 1000 mg DHA daily
- **GLA**—900 to 1800 mg daily
- **Vitamin E**—400 International Units (IU) daily with at least 200 mg gamma-tocopherol
- **Vitamin C**—1 to 3 grams (g) daily
- **Beta-carotene**—25,000 IU daily
- **Milk thistle (Silybum marianum)**—20 mg standardized to 70 to 80 percent silymarin
- **Natural progesterone**— $\frac{1}{4}$  to  $\frac{1}{2}$  teaspoon of cream twice daily on days 15 to 28 of the menstrual cycle
- **Indole-3-carbinol**—80 mg daily
- **Diindolylmethane (DIM)**—14 mg daily

## ENDOMETRIOSIS SAFETY CAVEATS

An aggressive program of dietary supplementation should not be launched without the supervision of a qualified physician. Several of the nutrients suggested in this protocol may have adverse effects. These include:

### Beta-Carotene

- Do not take beta-carotene if you smoke. Daily intake of 20 milligrams or more has been associated with a higher incidence of lung cancer in smokers.
- Taking 30 milligrams or more daily for prolonged periods can cause carotenoderma, a yellowish skin discoloration (carotenoderma can be distinguished from jaundice because the whites of the eyes are not discolored in carotenoderma).

## **EPA/DHA**

- Consult your doctor before taking EPA/DHA if you take warfarin (Coumadin). Taking EPA/DHA with warfarin may increase the risk of bleeding.
- Discontinue using EPA/DHA 2 weeks before any surgical procedure.

## **GLA**

- Consult your doctor before taking GLA if you take warfarin (Coumadin). Taking GLA with warfarin may increase the risk of bleeding.
- Discontinue using GLA 2 weeks before any surgical procedure.
- GLA can cause gastrointestinal symptoms such as nausea and diarrhea.

## **Milk Thistle**

- Consult your doctor before taking milk thistle with tranquilizers such as Haldol, Serentil, Stelazine, and Thorazine. Milk thistle combats the effect of tranquilizers.
- Do not combine milk thistle with the blood pressure medication Regitine. Milk thistle combats the effect of Regitine.

## **Progesterone**

- Do not take progesterone if you could be pregnant or are breastfeeding.
- Consult your doctor before taking progesterone if you have cancer of the reproductive organs.

## **Vitamin C**

- Do not take vitamin C if you have a history of kidney stones or of kidney insufficiency (defined as having a serum creatine level greater than 2 milligrams per deciliter and/or a creatinine clearance less than 30 milliliters per minute).
- Consult your doctor before taking large amounts of vitamin C if you have hemochromatosis, thalassemia, sideroblastic anemia, sickle cell anemia, or erythrocyte glucose-6-phosphate dehydrogenase (G6PD) deficiency. You can experience iron overload if you have one of these conditions and use large amounts of vitamin C.

## **Vitamin E**

- Consult your doctor before taking vitamin E if you take warfarin (Coumadin).
- Consult your doctor before taking high doses of vitamin E if you have a vitamin K deficiency or a history of liver failure.
- Consult your doctor before taking vitamin E if you have a history of any bleeding disorder such as peptic ulcers, hemorrhagic stroke, or hemophilia.
- Discontinue using vitamin E 1 month before any surgical procedure.

For more information see the Safety Appendix

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