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File: ■ Endometriosis

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RE: Herbal Medicine for the Treatment of Endometriosis

Stephens L, Whitehouse J, Polley M. Western herbal medicine, epigenetics, and endometriosis. *J Altern Complement Med.* 2013;19(11):853-859.

Endometriosis, a poorly-understood, estrogen-dependent condition affecting over 10% of Western women of reproductive age, is characterized by growth and presence of endometrial-like tissue outside the uterine cavity, usually around the pelvic organs and/or peritoneum. Extra-uterine endometrial tissue can cause severe pain. Several theories have been advanced for the occurrence of endometriosis but significant variability of symptom severity makes it likely to be multifactorial. Conventional management is based on reducing and preventing recurrence of pain with non-steroidal anti-inflammatory drugs (NSAIDs) and other analgesics, suppressing ovarian function with hormonal drugs, and surgical removal of endometriotic tissue. All have significant drawbacks. A new drug, dienogest, a 19-nortestosterone derivative, reports efficacy and tolerability; however, uncertainty over individual response rates still fuels interest in other approaches to management.

Herbal medicine has long been used in China for endometriosis, and its use is growing in the West. The UK's Royal College of Obstetricians and Gynaecologists reports that some women use complementary medicine, including herbs, to manage endometriosis either instead of hormone replacement therapy (HRT) or alongside conventional drugs. Several of the herbs commonly used have antiproliferative, antioxidant, anti-inflammatory, and/or analgesic effects in vitro. Difficulties with integrating herbs into a multidisciplinary approach, the authors say, stem from poor knowledge of herbal practice outside the herbalist community.

While herbal and conventional practitioners diagnose endometriosis using a common model of pathology, herbalists generally prescribe individual, frequently evaluated herbal regimens and lifestyle counseling. This individualized approach is supported by advances in understanding endometriosis' pathology. Immunological, hormonal, genetic, and environmental factors affect its development and progression, along with deregulation of several biological pathways. Epigenetic changes (in chromatin structure and gene expression not from DNA mutations) may be common denominators. Such changes may be reversed through lifestyle and environmental factors.

Some epigenetic changes seen in endometriosis are described, including aberrant methylation of promoter cell regions with either increased or reduced gene expression;

downregulation of gene expression by micro-RNAs (miRNAs), found in 48 of 487 miRNAs in endometriotic lesions; and histone modification. For example, chronic inflammation leads to hypermethylation of progesterone receptor B (PR-B) and progesterone resistance in endometriosis. Hypermethylation alters expression of PR-B and estrogen receptor β (ER- β). Hypomethylation of the ER- β promoter may induce progesterone deficiency. DNA methyltransferases (DNMTs) are overexpressed in endometriotic tissue as compared to control tissue. Endometriosis is heritable and persistent, and DNA methylation may explain how its aberrations are maintained.

MiRNAs regulate up to 30% of human genes. Downregulated miRNAs in endometriotic tissue include among their targets transforming growth factor β , estrogen receptor α , ER- β , and PR; changes in all of these are associated with endometriosis. MiRNAs affect inflammation, tissue repair, cell growth, proliferation, apoptosis, and angiogenesis. For example, miR-199a and miR-16 suppress cyclooxygenase-2 (COX-2). They are downregulated in endometriosis, raising levels of COX-2 and consequent inflammation. Meanwhile, increased expression of miR-15b/16 and miR-145 and downregulation of miR-20a, miR-221, and miR-222 are linked to increased survival of endometrial cells.

Herbs most frequently used for endometriosis at the University of Westminster's polyclinic are dong quai (*Angelica sinensis*), licorice (*Glycyrrhiza glabra*), poke (*Phytolacca americana*), gotu kola (*Centella asiatica*), calendula (*Calendula officinalis*), black haw (*Viburnum prunifolium*), celandine (*Chelidonium majus*), ginger (*Zingiber officinale*), yarrow (*Achillea millefolium*), lady's mantle (*Alchemilla xanthochlora* syn. *A. vulgaris*), thuja (*Thuja occidentalis*), milk thistle (*Silybum marianum* syn. *Carduus marianus*), henbane (*Hyoscyamus niger*), turmeric (*Curcuma longa*), and schisandra (*Schisandra chinensis*). All have shown antioxidant, anti-inflammatory, anti-spasmodic, antiproliferative/pro-apoptotic, and/or anti-nociceptive/analgesic effects relevant in endometriosis in vitro and/or in vivo. Some studies report positive effects on pelvic pain and inflammation with antioxidants. Overall, there is good evidence that commonly used herbs can positively affect the epigenome, potentially reversing the changes seen in endometriosis. Although there is a lack of clinical studies, existing research gives convincing evidence of their potential in this debilitating condition.

—Mariann Garner-Wizard

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