The Pains of Endometriosis

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Endometriosis is a disease defined by the presence of endometrial tissue outside of the uterus. Severe pelvic pain is often associated with endometriosis, and this pain can be diminished with therapies that suppress estrogen production. Many women with endometriosis also suffer from other chronic pain conditions. Recent studies suggest that mechanisms underlying these pains and sensitivity to estrogen involve the growth of implants and the pains associated with endometriosis, these pains may be due to the infiltration of the ectopic endometrial tissue of a nerve supply, which could have a varied and widespread influence on the activity of neurons throughout the central nervous system. Endometriosis is a common disorder that occurs mainly in women of reproductive age. Because ectopic endometrial implants respond to natural or induced decreases in estrogen levels, the disorder is considered “estrogen dependent” (1). Symptoms of endometriosis include reduced fertility and several types of pain such as severe dysmenorrhea (excessive menstrual pain), deep dyspareunia (pelvic pain with coitus), dyschezia (pelvic pain with defecation), and chronic pelvic pain. In some women, pain can be exacerbated by the co-occurrence of other severe chronic pain conditions such as irritable bowel syndrome, interstitial cystitis, repetitive kidney stones, vulvodynia, temporomandibular syndrome, migraine, and fibromyalgia (2–4). Little is known about the association between the ectopic implants and pain; however, recent studies of women and animal models are beginning to provide clues. The most common pharmacological treatment for endometriosis uses a class of drugs called gonadotropin-releasing hormone (GnRH) agonists. Because these drugs down-regulate GnRH receptors, they suppress pituitary gonadotropin secretion and sex steroid production, thereby producing a systemic hypoestrogenic state. This treatment results in the elimination or reduction in size of the implants in women (5) as well as in a rat model of endometriosis (6). In addition, optimized treatment with GnRH agonists is effective in reducing endometriosis-related pain symptoms in women (5). Because GnRH agonists reduce both implant size and the pains associated with endometriosis, these pains may be due to the presence of the abnormal implants. Numerous studies, however, have failed to find a correlation among pain scores, types of pain, and various aspects of the anatomy and biochemistry of the implants (7). In addition, although surgical removal of the ectopic implants alleviates pain symptoms in many women, the surgery can fail to alleviate the pain and/or pain may recur even without evidence of residual or recurrent disease or any other identifiable visceral or somatic pathology (8). On the other hand, correlations have been found between pain severity and both the depth of “infiltration” into peritoneum or pelvic organs and the proinflammatory cytokines, pros-
taglandins, chemokines, and other substances released by the implants or neighboring tissues into peritoneal fluid (1, 9). Of relevance here are findings that the percentage of patients reporting pain is greater in women with deeply infiltrating implants in highly innervated areas (such as the uterosacral region) than in women with other types of implants, and that the former implants are more likely to infiltrate nerves (10). Others have found that the nerve fibers are closer to the implants in women with pelvic pain than in women without pain (11). These results implicate the nervous system in the various pains of endometriosis. Indeed, recent results drawn from a rat model of endometriosis support this idea. This model (Fig. 1A) involves autotransplantation of parts removed from one uterine horn onto abdominal blood vessels, where the transplants then grow into cysts.

This rat model appears to be valid for studying both the signs of endometriosis (ectopic implants) and its symptoms (subfertility and pain). The implants in rats and women respond similarly to hormonal treatment and show similar alterations in protein production (12). Rats with endometriosis (ENDO rats), like some women with endometriosis, are subfertile (12). Although ENDO rats do not exhibit spontaneous pain behaviors (13), they develop an increased pain sensitivity (hyperalgesia) of the vagina, the severity of which correlates positively with estradiol levels during their ovarian cycle (14). Thus, ENDO rats suffer from a painful condition that is estrogen sensitive and is similar to dyspareunia in women. Furthermore, urinary bladder capacity is reduced in ENDO rats (14). In interstitial cystitis in women, the most salient symptom, other than pain, is excessively frequent urination. Endometriosis in rats also exacerbates pain behaviors associated with an artificial stone implanted in the ureter, and the stone in turn induces new pain behaviors like those that occur when the uterus is treated with an inflammatory agent (13). Thus, ENDO rats appear to develop pain symptoms similar to those associated with conditions that co-occur with endometriosis in women, specifically interstitial cystitis, uterine pain, and kidney stones (4).

The ectopic implants develop a sensory and sympathetic nerve supply both in rats (Fig. 1, B and D to F) and in women (Fig. 1, C and G to I), similar to that of the healthy rat uterus (15). In the rat model, this supply connects the implants directly with the central nervous system via the splanchnic and vagus nerves (14, 15). Input to the spinal cord from the implants arrives at the same spinal segments as those receiving input from the ureter (Fig. 1A, green shading), but rostral to segments receiving input from the vaginal canal (blue shading) or bladder (pink and blue shading). Thus, vaginal hyperalgesia and ureteral pain in this rat model likely involve central neural mechanisms [i.e., intersegmental spinal communication (14, 15)], whereas the effects of endometriosis on bladder function could be via peripheral interactions and/or in the caudal spinal cord.

Two other factors may help to explain the variable types and severity of endometriosis-associated pains, their co-occurrence with other painful disorders, and their amelioration by a hypoestrogenic state: (i) central sensitization, and (ii) divergent and convergent connectivity in the central nervous system. First, it is commonly recognized that sensory fibers of the type observed in both the rat and human ectopic implants (Fig. 1, F and I, respectively) are activated and sensitized by many inflammatory agents in them (1, 9, 16). By means of several molecular processes reviewed else-

![Fig. 1.](image-url)
where (16), sensitization of the sensory fibers would in turn produce central sensitization, which is a long-lasting hyperexcitability of neurons in the central nervous system that can continue long after the originally sensitized input is reduced or eliminated (e.g., by surgery).

Second, sensory input arriving at the spinal cord from individual internal organs diverges within the cord. Thus, although information from different organs is delivered most densely to spinal neurons within the entry segments, it is also delivered, less densely, to widespread spinal regions extending for many segments rostrally and caudally (14). The anatomical divergence gives rise to considerable convergence of information on central neurons. This “visceroviscero-somatic convergence” (13, 14) produces a situation in which the activity of somato-visceral neurons in the spinal cord and brain is dominated by information from individual peripheral structures but can be augmented, particularly in sensitized neurons, by events occurring elsewhere. Such convergence thereby provides a substrate by which sensitized input from ectopic implants augmenting that from healthy organs can have widespread influences on the activity of neurons normally associated with input from different individual organs and tissues, a situation that has been demonstrated in women (17). These results suggest that inconsistency in the various pains associated with the ectopic implants could reflect variability in a number of factors associated with the implants’ nerve supply. These factors include the types of nerves that innervate the implants, agents that activate or sensitize them, sites in the central nervous system where the nerves deliver information, and how that information is modulated by estradiol—both peripherally (18) and centrally (19)—as well as by other central dynamic processes (14, 17, 20).

Much remains to be learned about how endometriosis comes to be associated so variably with pain symptoms and how those symptoms are ameliorated by a hypoestrogenic state. One promising area of research concerns the implants’ sensory and autonomic nerve supply and its potentially estradiol-modulated influence on activity within the central nervous system.

References and Notes
2. M. Alagiri, S. Chottiner, V. Ratner, D. Slade, P. M. Hanno, Urology 49 (suppl. 5a), S2 (1997).
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Uterine Fibroids: The Elephant in the Room

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Uterine fibroids (leiomyomas) have historically been viewed as important chiefly as the major indication for hysterectomy. As new therapies are developed, the heterogeneity of this disease becomes therapeutically relevant. An awareness of the role of genetics, the extracellular matrix, and hormones in tumor etiology is key to understanding this disease.

Uterine fibroids (correctly called leiomyomas or myomas) are benign myometrial neoplasms enriched in extracellular matrix (ECM) (Fig. 1) (1). They are the primary indication for hysterectomy, accounting for over 200,000 hysterectomies annually in the United States, and are the cause of significant morbidity from profuse menstrual bleeding and pelvic discomfort. The range of clinical disease is extraordinary: Symptomatic lesions can be 10 mm in size or routinely exceed 20 cm. Tumors occur in 77% of women, and approximately 25% of Caucasians have clinically significant lesions (2). However, in African-American women, clinical disease is more severe and concordant with prevalence.

Rarer lesions such as the poor-prognosis leiomyosarcoma are providing insights into the biology of these benign tumors. Although it has been debated whether leiomyomas and leiomyosarcomas are part of a disease continuum, cytogenetic studies have demonstrated that chromosome rearrangements in leiomyomas are similar to those seen in other benign tumors but are distinct from the complex rearrangements and aneuploid karyotypes characteristic of leiomyosarcomas (3). However, recent microarray data from the Morton laboratory identified a rare subset of leiomyomas with deletions of chromosome 1 that have transcriptional profiles that cluster with those of leiomyosarcomas (4), suggesting that some uterine leiomyosarcomas may in fact arise from a specific subset of leiomyomas. There are also related lesions with both benign and malignant features. Benign metastasizing uterine leiomyoma is characterized by leiomyoma-like lesions, usually in the lungs, in women with fibroids. Lymphangioleiomyomatosis is a similar disease, affecting only women, in which the characteristic lung lesions originate from “benign” renal angiomyolipomas (5). Similarly, intravenous leiomyomatosis (IVL) is a hormonally responsive disease that causes venous extensions originating in the uterus that can extend as far as the heart. These leiomyomas have cytogenetic alterations similar to those seen in atypical lipomatous tumors that are locally invasive but do not metastasize (6).

Risk Factors and Prevalence

The prevalence of clinically significant fibroids peaks in the perimenopausal years and declines after menopause (7). Obesity and early age at menarche, which increase a woman’s overall lifetime exposure to estrogen, are known risk factors. The risk of developing fibroids is higher in African-American than in Caucasian women, and they often have more severe disease. Parity is also a significant risk factor, with age at the birth of the last child being inversely associated with risk, suggesting that pregnancy may remove nascent tumors or promote regression, as is thought to be the case with endometrial cancer. Pregnancy reveals the extraordinary extent to which myometrial smooth muscle cells (MSMCs) can grow without malignant transformation. One hypothesis, proposed by Barbieri and Andersen, is that