Treatment of pain associated with deep endometriosis: alternatives and evidence

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Pain is the most evident clinical manifestation of deep infiltrating endometriosis (DIE). Several hormonal and immunologic mechanisms are markedly altered in DIE compared with superficial peritoneal and ovarian endometriosis, and may explain its most aggressive behavior and the presence of severe pain symptoms. Hormonal therapies, such as combined hormonal contraceptives and progestogens, should be regarded as first-line treatment, as they are efficacious, safe, and well tolerated. Gonadotropin-releasing hormone agonists may be used in patients with symptoms persisting after the administration of first-line therapies. Scanty literature is available for danazol treatment in patients with DIE and, however, it has become less popular due to the high rates of androgenic adverse events (AEs). The partial relief of pain that often is achieved with available therapies and its recurrence after the suspension of the treatment have brought to the development of new therapies (such as aromatase inhibitors, oral GnRH antagonists) that are currently under investigation. Surgical excision of DIE should be considered in patients with pain symptoms persisting after first-line hormonal therapies. The benefits of surgery in terms of pain improvement should be always balanced with the risk of intraoperative complications and for this reason surgical cases should be referred to tertiary centers for the treatment of DIE. A multidisciplinary approach is mandatory in patients with DIE involving the bowel and/or the urinary tract. (Fertil Steril® 2015;104:771–92. ©2015 by American Society for Reproductive Medicine.)

Key Words: Deep endometriosis, endometriosis, medical treatment, pain, surgery

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Endometriosis is distinguished in three different phenotypes: ovarian endometrioma, superficial peritoneal endometriosis, and deep infiltrating endometriosis (DIE). Deep infiltrating endometriosis includes rectovaginal lesions as well as infiltrative forms that involve vital structures such as bowel, ureters, and bladder (1). It is the most severe form of the disease with an estimated prevalence of 1% in women of reproductive age (2). Deep infiltrating endometriosis is associated with very severe pain in >95% of cases, more often it includes dysmenorrhea, dyspareunia, nonmenstrual pelvic pain, and less commonly dyschezia and dysuria (1). Although plenty of treatments for DIE-associated pain are available (i.e., analgesics, anti-inflammatory drugs, hormonal therapies, surgery), these strategies offer, in most of the cases, only partial relief of symptoms (3).

The aim of this review is to offer the reader a complete overview of the alternative treatments for DIE-associated pain on the basis of the most updated available evidence.

BIOLOGICAL CHARACTERISTICS OF DIE

Several hormonal and immunologic factors are critically altered in DIE (4). Estrogen (E) biosynthesis is upregulated because of the increased expression of aromatase P450 (responsible for the conversion of androgens to E_2) (5) and of 17β-hydrosteroid dehydrogenase type 1 (responsible for the conversion of estrone [E_1] to E_2) (6). Furthermore, E inactivation is decreased because the activity of 17β-hydrosteroid dehydrogenase type 2, which converts E_2 to E_1, is downregulated (7). The expression of E and P receptors (ERs and PRs, respectively)

Received June 23, 2015; revised August 24, 2015; accepted August 25, 2015; published online September 10, 2015.
S.F. has nothing to disclose. F.A. has nothing to disclose. A.R. has nothing to disclose. U.L.R.M. has nothing to disclose.
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Fertility and Sterility® Vol. 104, No. 4, October 2015 0015-0282/$36.00

http://dx.doi.org/10.1016/j.fertnstert.2015.08.031

is altered in endometriosis. The unbalanced ER-β-to-ER-α ratio promotes a shift from E_2 stimulation to E_2 inhibition of PR expression (8, 9). This brings to an altered ratio between PR-B and PR-A isoforms and causes a resistance of the endometriotic tissue to the P's antiproliferative effects (10, 11). A recent study (12) showed that ER-α and PR-B are strongly expressed in rectovaginal endometriosis; this observation differs from previous researches on peritoneal and ovarian lesions. Single-nucleotide polymorphism in the promoter region of the human PR gene increases transcription of the PR-B form compared with the PR-A form (13). There is a significant association between the P receptor +331G/A polymorphism and DIE, suggesting a potential role of this variant in the P receptor-dependent invasive behavior of endometrial cells (14). Results from animal studies and cell culture experiments show that environmental toxicants may affect the pathophysiology of endometriosis (15–18). Exposure of mice to 2,3,7,8-tetrachlorodibenzo-p-dioxin leads to an epigenetic alteration, a P-resistant phenotype in adult animals that can persist for several generations (19). Deep infiltrating endometriosis shows a more aggressive behavior than other forms of endometriosis. An explanation of this may rely on the significantly decreased apoptosis and on the high proliferation activity related to oxidative stress in patients with DIE (20–22). Furthermore, DIE is characterized by higher expression of invasive mechanisms (matrix metalloproteinases and activins) and of neuroangiogenesis (nerve growth factor [NGF], vascular endothelial growth factor, and intercellular adhesion molecule) than superficial peritoneal and ovarian endometriosis (4). Considerable neuroangiogenic properties have been demonstrated in endometriotic lesions and peritoneal fluid (PF) from women with endometriosis, bringing to high expression of new nerve fibers, a shift in the distribution of sensory and autonomic fibers in some locations, and up-regulation of several neurotrophins (23). Direct innervation of endometriotic lesions by sensory and sympathetic fibers has been reported in animal models (24, 25) and in humans (26–29). Nerve fiber density seems to be higher in DIE than in peritoneal and ovarian lesions (30–35). Interestingly, nerve fiber density correlates with severity of pelvic pain or dysmenorrhea (29). Myelinated nerve fibers are present in rectovaginal nodules. A higher density of nerve fibers within the endometriotic nodules and a close histologic relationship between nerve fibers, endometriotic nodules, and fibrosis was reported in women with worse preoperative pain (30). The density of nerve fibers in DIE is higher than in peritoneal endometriosis and in rectal nodules than in other locations (31). An explanation for this peculiar nerve fiber density in DIE is still an object of investigation. A possible reason is that DIE often originates and develops in richly innervated anatomical locations. It can be speculated that proinflammatory reaction and high vascularization of the endometriotic implants in the presence of higher density of nerve fibers lead to more aggressive neuroangiogenesis than in other sites. Another explanation may lie in a higher capacity of DIE to induce nerve growth compared with other types of endometriosis, as supported by the higher expression of NGF and NGF receptors tyrosine kinase receptor-A (Trk-A) in DIE (33, 35). Nerve growth factor plays a key role in generating endometriosis-associated pain (36–38). Inflammation participates to this mechanism as NGF is up-regulated by inflammatory cytokines (i.e., tumor necrosis factor [TNF]-α and interleukin-1β), and is involved in persistent inflammatory pain by activating mast cell degranulation and cytokine production (39, 40). Deep infiltrating endometriosis contains more activated mast cells than peritoneal and ovarian endometriosis, and the mast cells appear to be in a closer relationship with nerves compared with other sites (41). On the basis of these findings, an interaction between local inflammation, immune system, and the presence of nerve fibers support a cellular and molecular and not just mechanical (endometriotic lesion/nerve compression) mechanism that justifies higher rates and more severe forms of pain in DIE compared with superficial peritoneal and ovarian endometriosis.

The ideal drug to treat DIE should act on the hormonal and immunologic environment, to down-regulate proliferation, to enhance apoptosis, and to renormalize the invasive mechanisms and neuroangiogenesis processes. Currently available treatment options for endometriosis (combined hormonal contraceptives, progestogens, and GnRH agonists), partially fulfill these requirements (42–53). Hormonal therapies (progestogens and combined hormonal contraceptives) decrease nerve fiber density, NGF and NGF receptor p75 expression in peritoneal endometriotic lesions (54). Progestogens and combined oral contraceptives (OCs) decrease the densities of sympathetic, parasympathetic, and sensory nerve fibers in DIE (55). The expression of E-regulated NGF and its receptor is only partially suppressed in patients using hormonal treatment, supporting that local E action is often preserved during therapy (55).

Clinical failure in the management of DIE and recurrence of pain symptoms are the two main criticisms associated with the use of available medical therapies. The development of new treatments targeting pathophysiological mechanisms (i.e., antiangiogenic agents, apoptotic agents, matrix metalloproteinase inhibitors, anti-inflammatory agents, sex steroids expression modulators) seems very attractive and has been the object of several researches. However, most of the agents have been tested in in vitro or in animal studies and their clinical application in humans is far from realized. Furthermore, many of these compounds are related to potential systemic and severe AEs, thus limiting their use in fertile young women (56).

MECHANISMS OF PAIN IN DIE

Endometriosis engages the central nervous system (CNS) creating a direct and two-way interaction between lesions and CNS itself. Growing evidence supports strict interaction between peripheral nerves, the peritoneal environment, and the CNS in pain generation and processing (57). Small, unmyelinated, nociceptive nerve fibers have been described in the functional layer of the endometrium of women affected by endometriosis and in ectopic endometriotic lesions (24,58–60). Nociceptive stimulus is transmitted through these nerve