Middle East Fertility Society Journal (2012) 17, 221–225

Middle East Fertility Society

Middle East Fertility Society Journal

www.mefsjournal.org
www.sciencedirect.com

OPINION ARTICLE

Pain and endometriosis: Etiology, impact, and therapeutics

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Received 31 July 2012; accepted 6 September 2012
Available online 18 October 2012

KEYWORDS
Endometriosis;
Dyspareunia;
Pelvic pain;
Social impact;
Quality of life;
Therapeutics

Abstract The association of pain and endometriosis was recognized with the first definitive published reports of this disorder. Unfortunately, the precise etiologies and pathways leading to nociception and pain symptoms in endometriosis remain poorly understood, and as a result, effective therapeutic interventions are lacking with consequent profound effects on affected women's quality of life. In this opinion paper we summarize selected proceedings presented at the 28th Annual Meeting of the European Society of Human Reproduction and Embryology (ESHRE) in Istanbul, Turkey, and review the clinical and translational evidence of chronic pain, neurogenesis, and the pernicious impact of dyspareunia on women with symptomatic endometriosis. The effectiveness of medical treatments is critically assessed and the findings indicate that good therapeutic options are available with extant medications effective in some sub-groups of women with endometriosis, many of which are affordable globally. Nevertheless, new management strategies and drugs need to be developed to increase the options of all afflicted women to minimize and ideally eradicate painful symptoms of endometriosis. However, only by elucidating distinctions among sub-groups with specific symptoms, suggesting different mechanisms, are we likely to derive truly successful therapeutic strategies.

1. Introduction

Endometriosis affects an estimated 176 million women worldwide between the ages of 15–49 (1) negatively influencing general physical, social and mental wellbeing during their most productive years (2). Pelvic pain has long been recognized as a critical concomitant of the endometriosis syndrome. Indeed, in Sampson's classic treatise (3), 12 of the 17 symptomatic cases he reported presented for surgery due to intolerable pain. Interestingly, as long ago as 90 years, he recognized that "there

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Peer review under responsibility of Middle East Fertility Society.

Production and hosting by Elsevier

1110-5690
http://dx.doi.org/10.1016/j.mefs.2012.09.002

is usually nothing characteristic about the pain present in this condition, nor is there necessarily any relationship between the extent of the adhesions and the severity of pain.'' This lack of correlation continues to confound modern era gynecologists (4), in large part because the mediators of painful stimuli in endometriosis are inadequately understood. In the June 2005 issue of the journal Science, a provocative and impactful publication in our field described the growth of efferent sympathetic and afferent sensory nerves into the ectopic implants of endometriosis in women and in a rat model of the disease (5). This paper by Berkley et al. (5) caught the attention of gynecologists, physiologists and neuroscientists alike, galvanizing trans-disciplinary efforts to evaluate the causes and develop new methods to ameliorate pain associated with endometriosis.

2. Symposium venue

In July 2012, a pre-congress symposium on ''Pain and Endometriosis'' was convened at the 28th Annual Meeting of the European Society of Human Reproduction and Embryology (ESHRE) in Istanbul, Turkey, to address this specific topic. The course represented an international collaboration between the Special Interest Group for Endometriosis and Endometrium (SIGEE) of ESHRE and the Endometriosis Special Interest Group (EndoSIG) of the American Society for Reproductive Medicine, and was organized and moderated by Professors Hilary Critchley (United Kingdom), Pamela Stratton (USA), Aydin Arici (Turkey), and Dr. Gerard Dunselman (The Netherlands). Its purpose was to consider clinical management, including accumulation of the best available evidence, and to provide mechanistic insights into the etiology of endometriosis-associated pain. A diverse, trans-disciplinary group of experts provided formal presentations. The editors of the Middle East Fertility Society Journal invited members of the World Endometriosis Society to relate some of those deliberations in this Opinion Paper.

3. Clinical and translational evidence

In her lecture entitled ''Chronic pelvic pain and endometriosis: Translational evidence of the relationship and implications'' Pamela Stratton, MD, Head of the Gynecology Consult Service at the National Institute for Child Health and Human Development (NICHD) in Bethesda, Maryland, USA, reviewed the clinical characteristics of chronic pelvic pain. These symptoms commonly overlap among gynecological and non-gynecological syndromes, including endometriosis, pelvic adhesions, leiomyomata and inflammatory bowel disease, making the precise attribution of pain difficult (6). She described current approaches to surgical treatment of endometriosis, based on the ''oncological principle'' to remove visible lesions and restore normal anatomy. As noted above, severity of symptoms correlates poorly with the extent of endometriosis and pain often recurs postoperatively even in the absence of visible new lesions. In only 50% of cases is pain relief sustained for more than a year after surgery; when pain recurs sooner, concomitant adenomyosis should be suspected. In the latter case, thickness of the junctional zone by magnetic resonance imaging may be informative (7). For medical management of endometriotic pain, it was noted that hormone treatments are not effective in all women and that leuprolide (a GnRH analog) may be effective in reducing pain even if it is not of endometriosis origin. Dr. Stratton's interesting placebo-controlled trial of raloxifene was presented. Based on its anti-estrogenic effects on endometrium and breast in animal and clinical studies, it was anticipated that this SERM might effectively suppress postoperative recurrence of pain from endometriosis. But in the 47 women randomized to up to 2 years of raloxifene (180 mg/day) following laparoscopic treatment of endometriosis, there was a significantly more rapid return of pain than the 46 subjects receiving placebo (8). Other pain studies from NICHD indicated that while migraine headaches might share pathophysiological pathways with endometriosis-associated pain, their prevalence was no greater in women with than those without endometriosis (9). Complex modeling, such as the Markov method, has been used to examine the lifetime utilization and perceived benefits of medical and surgical treatments for endometriosis-related symptoms. Using cross-sectional, self-reported survey data from 1160 women responding to the 1998 US Endometriosis Association survey, more than 40% had tried three or more different medicines and had three or more surgical procedures (10). The lecture concluded with a discussion of nociception (pain sensation) and sensitization of endometriotic lesions, modified by descending central nervous system pathways. The implications of myofascial trigger points and signs of sensitization including hyperalgesia, allodynia, and decreased pain pressure thresholds (PPT) were described as part of an ongoing study at NICHD. The preliminary data indicate that sensitization to pain is common in women with endometriosis, as well as in those with chronic pelvic pain without evidence of endometriosis (11). Dr. Stratton stressed that it will be important to extend our concepts beyond the endometriotic lesion per se, taking into account the complex influences of central afferents on nociception, if we are to improve the treatment of endometriosis-associated pelvic pain.

4. Fundamental mechanisms of neurogenesis in endometriosis

As noted above, microscopic studies have documented nerve fibers in endometriotic peritoneal lesions (12–14), deep infiltrating endometriosis (15,16), and ovarian endometriomas (17). Robert Taylor, MD, PhD, Vice Chair for Research in the Department of Obstetrics and Gynecology, Wake Forest School of Medicine, Winston-Salem, NC, USA, described the significance of interactions between the immune and neurovascular systems in endometriosis. Analyses from two independent groups demonstrated dense networks of nerve fibers in the superficial eutopic (intrauterine) endometrium of patients with endometriosis, whereas only rare nerves were found in women without disease (18–20). The histological identification of nerves has been proposed as the basis for a sensitive ($>90\%$), minimally invasive screening tool to identify women with endometriosis (18,20,21). Moreover, differences in endometrial nerve fiber density between normal women and those with endometriosis provide a plausible explanation for the pain associated with endometriosis (20–22).

Few studies of endometrial neurogenesis in endometriosis have been undertaken, but research involving nerve growth in other aspects of mammalian physiology has identified several different neurotrophin (NT) proteins that promote neuron