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Obstacles and Pitfalls of Endometriosis-Related Chronic Pelvic Pain Management: Trying to Alleviate the Burden

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Abstract

Chronic Pelvic Pain (CPP) could be defined as the presence of non-cyclic pain of 6 months duration or longer that localizes to the pelvis and is severe enough to cause functional disability and require medical or surgical treatment. Among women who undergo laparoscopy for CPP, endometriosis results in approximately 1/3 of the cases; conversely, among women who do not have CPP, endometriosis is present in only 5% of cases. Moreover, accumulating evidences support the opinion for which CPP has poor correlation with endometriosis stage, moderate correlation with isolated presence of ovarian endometrioma, strong correlation with Deep Infiltrating Endometriosis (especially if it affects bowel or urinary tract) and/or adhesion. Endometriosis-related CPP could arise through different pathways: one of the clearest reason is that endometriotic lesion could provoke a compression or infiltration of nerves; another possible causes of arising CPP could be represented by the increase of Nerve Growth Factor (NGF) in the endometriotic lesion area; last but not least, CPP could arise and be exacerbated also by inflammation of the peritoneal microenvironment. The hormonal therapies do not eliminate the endometriotic implants and, for this reason, stopping the treatment pelvic pain and other typical symptoms of endometriosis may recur and exacerbate the pre-treatment condition. The surgical treatment of endometriosis-related CPP is still not perfectly encoded, due to the unclear etiology and the different response to therapies. For these reasons, there is necessity of more efforts to create new non-invasive strategies that set a more accurate diagnosis and treatment of the causes of endometriosis-related CPP.

Keywords: Endometriosis; Chronic pelvic pain; Diagnosis; Medical treatment; Surgical treatment

The Dimension of the Problem

Chronic Pelvic Pain (CPP) could be defined as the presence of non-cyclic pain of 6 months duration or longer that localizes to the pelvis and is severe enough to cause functional disability and require medical or surgical treatment [1]. It could be considered nowadays a deep health problem that challenges physicians all over the world. This because its aetiology is still unclear, the course of the disease could vary a lot among different patients and through time in the same patient, and the response to treatments is not every time successful. CPP affects deeply and negatively woman's quality of life, contributing not only to suffering, but also to marital and family problems, to problems related to the achievements of work tasks, and overall to disability in woman's role in modern society. Mathias et al. reported that among 5,263 U.S. women, 773 (14.7%) had CPP within the past 3 months, and that in 61% of the cases the aetiology was unknown. They underlined also that women diagnosed with endometriosis reported the most health distress, pain during or after intercourse, and interference with activities because of pain. It represents also a public financial problem, because deeply increases medical cost for diagnosis and therapy: just considering USA, it costs approximately $881.5 million per year [2]. CPP aetiology could be related to different disease, such as urologic (recurrent and/or interstitial cystitis, complication after urologic surgery, nephrolithiasis, urolithiasis), gastrointestinal (irritable bowel syndrome, chronic inflammatory bowel disease, diverticulosis, polyposis), vascular, musculoskeletal, neurological, psychological. For this reason, actually the world medical literatures suggest to engage a multidisciplinary approach to this syndrome [3]. Just considering gynaecological and obstetric point of view, CPP could arise from a wide range of conditions, included presence of adhesions that can involve pelvic organs and walls, chronic cervical infection for cervical stenosis, post-surgical complication after cryo/laser/diathermy surgery for portio diseases, Pelvic Inflammatory Disease (PID), endometriosis and adenomyosis. Recent estimates suggest that in nearly 1/3 of the cases the reason for the pain seems to be due to endometriosis and in another third to adhesions [4]. According to Howard [5] there are four of more common disorders associated with chronic pelvic pain (endometriosis, adhesions, irritable bowel syndrome, and interstitial cystitis). Moreover is it widely accepted that CPP could be due also to coexistence of interstitial cystitis and endometriosis in the same patient, the so-called "Evil Twins Syndrome". In order to assess the incidence of this condition, Chung et al. [6] collected 178 women with CPP who presented with bladder base/anterior vaginal wall and/or uterine tenderness, with or without irritative voiding symptoms. They found presence of endometriosis in 134 (75%) patients, and of interstitial cystitis in 159 (89%) patients. So, they suggest performing both laparoscopic and cystoscopic examinations concurrently with the patient anesthetized in the initial evaluation and treatment of CPP, in order to avoid unnecessary delay in making the diagnosis. The strict connection between urological and gynaecological diseases in the arising of CPP is confirmed also by another work by Stanford et al. [7], who collected 64 patients who underwent intravesical potassium sensitivity test (PST), cystoscopy with double-fill hydrodistension, physical examination for vulvar pain, pelvic pain/urgency/frequency (PUF) screening questionnaire and laparoscopy to assess the presence of peritoneal pathology. Their results seems to evidence that bladder pain, peritoneal pathology, and vulvar pain are independent risk factors of CPP, although a trend of severity was noted in patients who had worse symptoms (increased voids per day, urgency, pain, and PUF scores).

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Endometriosis and Chronic Pelvic Pain: A Strict Connection

Endometriosis is an estrogen-dependent disease [8] characterized by the ectopic presence and growth of functional endometrial tissue, glands, and stroma, outside the uterine cavity [9,10].

The disease most often affects the ovaries (up to 88% of all cases), uterine ligaments, fallopian tubes, rectum, cervical-vaginal region, and urinary tract. Urinary tract involvement is rare accounting for around 1-2% of all cases [11-13], of which 84%are found in the bladder [14]. However, endometriosis can be encountered in other abdominal organs such as the liver, pancreas, intestinal tract, spleen [15], gallbladder [16], the abdominal wall, and even the navel [17]. Endometriosis is classified depending on the number, size, and superficial and/or deep location of endometrial implants, plaques, endometriomas, and/or adhesions, as follows: stage I (minimal, 1-5 points), stage II (mild, 6-15 points), stage III (moderate, 16-40 points), and stage IV (severe, >40 points), following the revised American Society for Reproductive Medicine classification for Endometriosis [18]. Exerting a gross classification, endometriotic lesions could be divided into superficial peritoneal endometriosis, deeply infiltrating endometriosis (DIE) and ovarian (cystic) endometriosis [19]. Approximately 10% of women in reproductive age are estimated to be affected by this disease and its symptoms [20,21]. In particular, pelvic pain could be expressed in a wide range combination of type, such as dysmenorrhea, dyspareunia, dysuria, dyschezia, non-menstrual chronic pelvic–abdominal muscle pain [22]. In particular, accumulating evidence seems to confirm that; dysmenorrhea is independent of the macroscopic type of the lesions or their anatomical locations and may be related to recurrent cyclic micro bleeding in the implants [23]. According to Faucconier's group [24,25], only DIE lesions are associated with CPP, especially when this type of lesions involve bowel or urinary tract. Moreover, they found that endometriosis appears to be responsible for chronic pelvic pain symptoms in more than half of histologically confirmed cases [23]: nevertheless, it is very important to understand if CPP is caused by endometriosis, or endometriosis and CPP are separated entity. Among women who undergo laparoscopy for CPP, endometriosis results in approximately 1/3 of the cases; conversely, among women who do not have CPP, endometriosis is present in only 5% of cases [24-26]. Moreover, accumulating evidences support the opinion for which CPP has poor correlation with endometriosis stage [27], moderate correlation with isolated presence of ovarian endometrioma [28], strong correlation with DIE (especially if it affects bowel or urinary tract) [24] and/or adhesion [29]. The discrepancy observed between endometriosis stage and severity of CPP may be due to variable roles of different endometriosis-related pain mechanisms [30], and, in our opinion, also to the different influence that each mechanism have on the others. It is widely accepted in literature that there is no significant correlation between pain level and presence and size of ovarian endometriomas and extent, type, and site of peritoneal lesions [31]. Other Authors [32], on the contrary, state that endometriosis-related CPP could depend on location of endometriotic lesions. Similar finding was found by Arruda et al. [33] in a cohort of Brazilian women, in which endometriosis symptoms (especially CPP) were more severe in young women with delayed diagnosis. Considering that pain attributed to endometriosis occur even in women without endometriosis and pain and severity correlate poorly with lesion characteristics, accumulating evidence suggest that the diversified experience of pain may be due to the pain modulation activity of the Central Nervous System (CNS) [22].

Endometriosis-Related Chronic Pelvic Pain Pathways

Endometriosis-related CPP may be due to nociceptive, inflammatory, or neuropathic mechanisms, and probably all three of these mechanisms are important and interdependent [34]. Nociceptive stimuli could be exacerbate or decrease by reproductive (and consequently hormonal) status of the patient. In particular, estradiol (E2) is the best-defined mitogen for the growth and inflammation processes in the ectopic endometriotic tissue. The counterpart, represented by progesterone and progestins, is actually widely used in therapy to control endometriosis symptoms, both before and after surgery. Although the good result achieved with progestings, a portion of patients do not respond to this kind of treatment. This fail is probably related to overall reduction in the levels of progesterone receptors (PRs) and, in particular, to the lack of the PR isoform B (PR-B) typical of endometriotic implants [35]. On the other hand, progesterone resistance could depend, at least in part, by a loss of coregulation by Kruppel-like factor 9 (KLF9) on WNT-signaling component in human endometrial stromal cells [36]. Apart from the local environmental/inflammatory condition which could account for pain arising, CNS and Peripheral Nervous System (PNS) seem to influence each other, because CNS neurons responsive to stimulation of the reproductive tract also respond to stimulation of skin and other pelvic organs. Since this, it was observed a dynamic interconnection of these different stimuli entering the CNS via gateways through the spinal cord, dorsal column nuclei, and solitary nucleus, which can finally orchestrate the final response and pain perception of the patient [37]. CPP could arise through different pathways: one of the clearest reason is that endometriotic lesion could provoke a compression or infiltration of nerves [38]. Other possible causes of arising CPP could be represented by the increase of Nerve Growth Factor (NGF) in the endometriotic lesion area, and this may worse the disease progression by two different way: on one hand it could improve "neural sprouting" and so create new painful afferents to the CNS, and, on the other hand, it could be considered itself a mediator that may exacerbate the CPP [39]. Moreover, accumulating evidence seems to confirm that endometriotic lesions could stimulate the growth of their own innervations by sensory and sympathetic fibers. CPP itself (related or not to endometriosis) seems to be associated with a distinctive pattern of proliferation of small-diameter nerve fibers through the myometrial stroma of uterus [40]. Interestingly, some authors [41] found that this innervations is denser in DIE lesions respect to other lesion type (and this could make relation with the fact that DIE lesions are frequently associated to CPP respect to other lesions type), although Others [42], on the contrary, state that there are no differences in detection of peritoneal "neural sprouting" (using immunocytochemistry staining with an antibody for neurofilament) between endometriotic patients and controls. Another cell mediator, the Vascular Endothelial Growth Factor (VEGF), could contribute to neoangiogenesis of the nerve vessels (in order to support "neural sprouting"), and so could enhance CPP [43]. Last but not least, CPP could arise and be exacerbated also by inflammation of the peritoneal microenvironment: in endometriosis immune alterations occur in the Peritoneal Fluid (PF) and peripheral blood, in part comparable to those proper of autoimmune diseases. It is widely reported an increase in the number but not in the function of macrophages, abnormalities in the functions and numbers of T and B lymphocytes, a reduction in number and activity of natural killer cells, apoptosis impairment, changes of cytokines and other soluble products in the peritoneal microenvironment [44-46]. In fact, it was showed a prevalence of Th1 profile (inflammatory) cytokines in the PF of women with endometriosis at minimal and mild stages whereas a Th2 profile (profibrotic, proangiogenic) cytokines prevailed in severe stages [47,48]. Moreover it was reported that the Fas/FasL apoptosis pathway system is dysregulated progressively throughout the course of the disease, with the result that endometriotic cells do not undergo

Fas/FasL-mediated apoptosis because they do not receive a death signal from Peritoneal Fluid Mononuclear Cells (PFMCs), so implanting themselves and surviving outside of the uterus. Paradoxically, endometriotic cells become themselves capable of killing PFMCs and this may allow their establishment in the peritoneum, which in turn becomes an immune privileged environment [49].

Medical Treatment

Usually, the first step in treatment of CPP (related or not to endometriosis) is represented by analgesic drugs, but this medical treatment seems to be not effective, or, at least, there is no evidence that can alleviate pain in every patient. Among hormonal therapy, many drugs were tested to treat endometriosis: combined oral contraceptives (OCs, estrogens and progestins) [50], danazol [51], gestrinone, medroxyprogesterone acetate [52] and GnRH agonists have good chance to reduce endometriosis-related CPP, and have equal effectiveness to suppress ovarian production of estrogens and progesterone [53]. In particular, Szendei et al. [27] found that after laparoscopic surgery for endometriosis, the use of monophasic OC treatment could significantly reduce pain scores and the necessity of other radical operative solution. This finding is shared also by Gambone et al. [53] who moreover state that for women in whom endometriosis is the suspected cause of CPP the best approach seems to use medical therapy, including second-line therapies such as danazol, GnRH agonists, and progestins until there is necessity for surgery. The rational of using progestins combined or not with estrogens is related to two different actions: on one hand, their anti-angiogenic, immunomodulatory and anti-inflammatory effects, and, on other hand, their action of inhibition of implantation and growth of refluxed menstrual endometrial debris [54]. About other kind of hormonal therapy, Leuprolide acetate (GnRH agonist) could be effective as pain reliever in women with endometriosis-associated CPP, although some Authors [55] state that it could be effective also in CPP in women without endometriosis. Also Intra Uterine System with Levonorgesterl (LNG IUS) could be useful and decrease endometriosis-associated CPP [56]. In any case, the hormonal therapies do not eliminate the endometriotic implants and, for this reason, stopping the treatment pelvic pain and other typical symptoms of endometriosis may recur and exacerbate the pre-treatment condition. New therapeutic strategies aimed at restoring PF homeostasis of the, through suppression of the production of proinflammatory cytokines such as TNFα, aromatase inhibition, and restriction of neoangiogenesis and "neural sprouting" [26,44]. In particular, a large body of evidence indicates that TNFα involved in macrophage activation, inflammatory change, and enhanced angiogenesis to develop endometriosis [57]. In addition to its proinflammatory functions, TNFα also stimulates the expression of matrix metalloproteinases in endometrial tissue [58], which are weel-known to play a key- role in tissue remodeling and invasion of endometriotic lesions [59]. Confirming these assumptions, TNF-α-targeted suppression by specific drugs inhibits the development of endometriosis in baboons [60,61]. Regarding aromatase, the rate-limiting enzyme for the synthesis of estrogen, a bunch of evidence suggests that is aberrantly expressed in endometriotic implants. Epigenetic changes favoring the transcription of the aromatase gene in the endometrium allow endometrial cells to survive in ectopic locations by producing estrogens that spare them from destruction through activated macrophages [62,63]. So, in our opinion, also aromatase inhibitors could be considered a promising way of treatment (associated or not with other conventional therapy) to relieve endometriotic-associated pelvic pain.

Surgical Treatment

The surgical treatment of endometriosis-related CPP is still not perfectly encoded, due to the unclear etiology and the different response to therapies. Among the surgical techniques, laparoscopy is efficient for ovarian endometrioma excision or utero-sacral ligaments and vaginal deeply infiltrating endometriosis [64], whereas for massive bowel or bladder endometriotic lesions it could be useful open surgery (especially for surgeons who are not fully dedicated to gynecological mini-invasive surgery) or robotic surgery [65]. The most important concept approaching to endometriosis surgery is that excision of the lesions must be radical and complete, in order to restore proper anatomy and function of the pelvic organs [66]. Surprisingly, Sutton et al. [67] showed that CPP return sooner after surgery in patients with endometriosis at minimal and mild stages. Despite radical surgery, some Authors [64] found that pain re-arise and the patients undergo reoperation in 50-60% of the cases by 5 - 7 years. There is also evidence that re-operations rates are lower after hysterectomy than after operative laparoscopy [68], probably because uterus contain a great number of neural elements that can contribute to arising and exacerbation of CPP. The presence of thick adhesions could represent a marker of easy reforming lesions and consequently lesion associated CPP, respect to thin adhesions [69]. Moreover, deep dyspareunia is strongly correlated with the presence of dense pelvic adhesions [70]. About this, a Cochrane review [71] stated that adhesiolysis was not associated with an improved outcome on CPP apart from where adhesions were severe. Confirming this finding, Li et al. [72] analyzing 662 patients with endometrioma and pelvic adhesion undergoing laparoscopic ovarian endometrioma excision, found that endometrioma adhesion rate is related to severer pelvic pain symptoms, and that postoperative pain recurrence rate is more frequent in patients with moderate-to-severe endometrioctic adhesion. Moreover, DIE lesion excision seems to have more effectiveness in long-term pain relief [53] respect to treatment of endometriomas and superficial peritoneal endometriosis [25,73]. Nevertheless, there is evidence that the superficial peritoneal lesions and adhesions, if not excised, represent a risk of CPP recurrence [69]. Regarding to the various surgical techniques that could be used, the Laparoscopic Utero-Sacral Nerve Ablation (LUNA) and the Presacral Neurectomy (PNS) seem to be effective to manage CPP, although pain recurrence are very frequent. Vercellini et al. [74] suggests that presacral neurectomy and amputation of the uterosacral ligaments seems to be uneffective to treat endometriosis-related CPP and does not demonstrate better results with the use of lasers rather than electrocoagulation. Also others agree with these assumptions [75], and moreover suggest using LUNA also for control of chronic pelvic pain without evidence of endometriosis. Confirming this result, Johnson et al. [76] found that there is a significant reduction in dysmenorrhea at 12 months follows up in women with chronic pelvic pain in the absence of endometriosis who underwent LUNA, but no significant difference in non-menstrual pelvic pain, deep dyspareunia or dyschezia. About the comparison between the two techniques, it seems that the short term results for PSN and LUNA seem to be similar, although PSN has better results in the long term [77]. Some good results about PSN came from data of Jedrzejczak et al. [78] and Zullo et al. [79] who evidenced that this technique could promote long-term pain relief. Kanazi et al. [80] suggest also another surgical nerve-blocking technique to treat endometriosis-related CPP: they blocked superior hypogastric plexus (SHP) and found that all patients had significant pain relief immediately after the block, although the pain scores postblock ranged from 0 to 4/10 and the duration of pain relief varied from 1 to 14 days. In order to allow easier, safer, and more accurate needle placement in SHP, Waldman et al. [81] use a single needle placed under computed tomography guidance. About this, as last standing solution, Kapural et al. [82] suggest to use the spinal cord stimulation (SCS) to treat chronic pelvic pain of visceral origin: they found, after this technique,

a reduction of the Pain Disability Index (PDI) score and of the opioid drug use. Same conclusion about this technique seems to be shared by Martellucci et al. [83] Finally, like is evidenced by Carter [84], with application of all currently available laparoscopic modalities, 80% of women with chronic pelvic pain will report a decrease of pain to tolerable levels, a significant average reduction which is maintained in 3-year follow-up.

Alternative Therapies

Some patients affect by CPP could have an aetiology derived from psychiatric diseases that vent their devastating symptoms on the pelvic area, from drug addiction or rebound phenomena to the drug use. The physician who approaches women with CPP must also keep in mind that it is often associated to migraine and headache, regardless if related or not to endometriosis [85]. Moreover, patients with diffuse abdominal/pelvic pain had more traumas and worse mental and physical health status compared with patients with vulvovaginal pain and cyclic pain, and also had poorer health than patients with neuropathic and fibroid pain [86]. So, when all possible anatomical/functional causes of CPP are excluded, is recommended to address patient to counseling or psychotherapy [71,87], although Others [84] suggest however to address patients affected by endometriosis-related CPP to this approach because pain could be due, at least in part, to psychological features. About this, it was showed that there are no differences in mood symptoms or personality characteristics between patients with endometriosis-related CPP and with CPP not associated with endometriosis, but women with endometriosis had more severe pain and greater social dysfunction than those with unexplained pain [88]. Confirming this, Lorençatto et al. [89] evaluated 100 women with endometriosis, equally divided into one group suffering from CPP and the other pain-free. Using Beck Depression Inventory (BDI), they detected depression in 86 and 38% of the women with and without chronic pelvic pain, respectively, and so they concluded that depression is highly prevalent in women with endometriosis, especially those with pelvic pain. On the light of these results, it is widely accepted that biobehavioral techniques such as relaxation and biofeedback can help patients modifying their experience of pain [90]. Finally, some authors [91] suggest that electrodermal measures at Jing-Well acupuncture points ("indicator" points located at the tips of fingers and toes) are associated with clinical outcome in adolescent women with endometriosis-related CPP, and that acupuncture treatments could reduce this important symptoms.

Conclusion

The endometriosis nowadays seems to stand out among the causes of this pain syndrome, although currently the efforts of the medical world are intended to clarify clearly and definitively the causal relationship between the two diseases. It seems, in fact, that the phenomena induced by endometriosis in the pelvis, including the breakdown of peritoneal homeostasis and the induction of the production of proinflammatory and proangiogenic cytokines, are responsible of altered innervations and modulation of pain pathways in these patients. Although the good results achieved so far, there is necessity of more efforts to create new non-invasive strategies that set a more accurate diagnosis of the causes of endometriosis-related CPP, in order to improve and address the best pathway to manage this painful syndrome.

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