



New Treatment Modalities for Chronic Pelvic Pain

Rukset Attar MD., PhD.
Yeditepe University Hospital
Department of Obs and Gyn

Definition

- Chronic pelvic pain is defined as pain that occurs below the umbilicus that lasts for at least six months and is severe enough to cause functional disability or require treatment.
- It may or may not be associated with menstrual periods.
- Chronic pelvic pain may be a symptom caused by one or more different conditions, but in many cases is a chronic condition due to abnormal function of the nervous system (often called “neuropathic pain”).

Prevalance

- The prevalence of CPP ranges from 4 to 16 percent, but only about one-third of women with CPP seek medical care
- It is considered the principal indication for approximately 20 percent of hysterectomies performed for benign disease and at least 40 percent of gynecological laparoscopies

Causes Of Chronic Pelvic Pain

- A variety of gynecologic, gastrointestinal, urologic, musculoskeletal and body-wide disorders can cause chronic pelvic pain

Causes Of Chronic Pelvic Pain

- Gynecologic causes
 - **Endometriosis** - the most common diagnosis; about one-third of women who undergo laparoscopy because of CPP are diagnosed with endometriosis
 - **Pelvic inflammatory disease** - Two factors correlate with the likelihood of developing CPP severity of adhesive disease and tubal damage (eg, hydrosalpinx)
 - persistent pelvic tenderness 30 days after diagnosis and treatment
 - However, the underlying reason that PID often leads to CPP has not been clearly established

Causes Of Chronic Pelvic Pain

- Gynecologic causes
 - Pelvic adhesive disease
 - Pelvic congestion syndrome — Pelvic congestion syndrome is a controversial entity
 - Adenomyosis
 - Ovarian cancer
 - Ovarian remnant and residual ovary syndrome
 - Leiomyoma
 - Vulvar pain and dyspareunia
 - Dysmenorrhea

Causes Of Chronic Pelvic Pain

- **Non-gynecologic causes of chronic pelvic pain**
 - may be related to the digestive system, urinary system, or to pain in the muscles and nerves in the pelvis
 - Irritable bowel syndrome
 - Painful bladder syndrome and interstitial cystitis
 - Diverticulitis
 - Pelvic floor pain
 - Abdominal myofascial pain (trigger points)
 - Fibromyalgia
 - **Coccydynia, piriformis/levator ani syndrome, pelvic floor tension myalgia**
 - **Osteitis pubis**
 - **Mental health issues** — Mental health disorders, especially somatization disorder, drug seeking behavior and opiate dependency, physical and sexual abuse experiences, and depression

Chronic Pelvic Pain Treatment

- To decide on the best therapeutic plan for an individual patient, the physician and patient should have a thorough discussion of her preferences and values regarding testing, medical versus surgical treatment, and childbearing plans.
- For many patients, the optimal approach involves a combination of treatments.

Chronic Pelvic Pain Treatment

- **Empiric trial of therapy based on diagnostic probabilities** - One approach to managing women with CPP is to prescribe sequential drug treatments for disorders that are the most likely causes of the patient's CPP.
- **Intensive diagnostic evaluation followed by targeted therapy** — A different approach is to use intensive diagnostic testing in an attempt to identify the specific cause of the patient's CPP, if possible, before starting specific therapy
- **Nonspecific analgesia** — A third option is treatment directed at pain, rather than at a specific diagnosis

Chronic Pelvic Pain Treatment

- Medical treatment
- Physical therapy
- Behavioral medicine
- Neuromodulation
- Interventional-Pain management clinics
 - Acupuncture
 - Biofeedback and relaxation therapies
 - Nerve stimulation devices
 - Injection of tender sites with a local anesthetic (eg, lidocaine, Marcaine)
- Surgical treatment

Chronic Pelvic Pain Treatment

- Optimal patient outcomes often result from multiple approaches utilized in concert, coordinated via a multidisciplinary team of pain specialists

Chronic Pelvic Pain Treatment

- Medical Therapy
 - Non-opioid analgesic agents (eg, aspirin, acetaminophen, nonsteroidal anti-inflammatory drugs [NSAIDs], COX-2 Inhibitors)
 - Tramadol
 - Opioids
 - Alpha 2 adrenergic agonists
 - Antidepressants (tricyclics and serotonin-norepinephrine reuptake inhibitors [SNRIs])

Chronic Pelvic Pain Treatment

- Medical Therapy
 - Antiepileptic drugs (gabapentin, pregabalin, and other anticonvulsants)
 - Muscle relaxants
 - N-methyl-d-aspartate (NMDA) receptor antagonists
 - Topical analgesic agents

Chronic Pelvic Pain Treatment

- The choice of an appropriate initial therapeutic strategy is dependent upon an accurate evaluation of the cause of the pain and the type of chronic pain syndrome.
- In particular, neuropathic pain should be distinguished from nociceptive pain

Chronic Pelvic Pain Treatment

- Neuropathic pain, resulting from damage to or pathology within the nervous system, can be central or peripheral.
 - Causes of neuropathic pain are multiple, and include diabetes mellitus, postherpetic neuralgia, and stroke.
- Nociceptive pain, in contrast, is caused by stimuli that threaten or provoke actual tissue damage.

Nociceptive pain is often due to musculoskeletal conditions, inflammation, or mechanical/compressive problems

Chronic Pelvic Pain Treatment

- Neuropathic pain
 - treatment targeted to the specific diagnosis - if nerve function is impaired by compression or drugs, alleviating the compression or removing the offending agent
 - the initial treatment of neuropathic pain involves either antidepressants (tricyclic antidepressants or dual reuptake inhibitors of serotonin and norepinephrine) or calcium channel alpha 2-delta ligands ([gabapentin](#) and [pregabalin](#)), with adjunctive topical therapy (eg, topical [lidocaine](#)) when pain is localized ([algorithm 1](#)).
 - Opioids should be considered a second-line option.

Chronic Pelvic Pain Treatment

- In contrast to neuropathic pain, the pharmacologic approach to nociceptive pain primarily involves non-narcotic (acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs)) and opioid analgesia.
- Medication is used in conjunction with nonpharmacologic therapies and approaches to relieve the source of the pain.

Endometriosis Associated Pain

- Dysmenorrhoea
- Dysparonia
- Dysuria
- Dyschesia
- Painful gastrointestinal symptoms
- Nerve entrapment pain

Endometriosis Associated Pain

- Although the association of pain and endometriosis is widely accepted by gynecologist, the nature and characteristics of the pain related to endometriosis is poorly understood.
- Widespread endometriosis can be found in largely asymptomatic women, whereas small amounts of endometriosis appear to cause intractable pelvic pain in others

Endometriosis Associated Pain

- The most commonly suggested mechanisms for pain production in endometriosis are;
 - production of substances such as growth factors and cytokines by activated macrophages and other cells associated with functioning endometriotic implants
 - the direct and indirect effects of active bleeding from endometriotic implants
 - irritation or direct invasion of pelvic floor nerves by infiltrating endometriotic implants, especially in the culde- sac

Endometriosis Associated Pain

- more elusive mechanisms such as neuroangiogenesis, nociceptive, or neuropathic mechanisms are likely to contribute

Treatment of Endometriosis Associated Pain

- Current therapy aims to reduce the pain and to delay recurrence for as long as possible.
- The disease recurs after cessation of treatment, underlining the importance of developing new treatment strategies

Treatment of Endometriosis Associated Pain

- Aromatase inhibitors
- Melatonin inhibitors
- Angiogenesis inhibitors
- Matrix metalloproteinase inhibitors
- RU486 (mefipristone)
- Selective progesterone receptor modulators
- Selective estrogen receptor modulators
- GnRH antagonists

Aromatase inhibitors

- The first report describing the use of an aromatase inhibitor in the treatment of endometriosis was by Takayama *et al* in 1998
- 57-year-old woman with recurrent severe endometriosis after hysterectomy and bilateral salpingoophorectomy with oral anastrozole for 9 months
- They reported a significant reduction in pelvic pain and lesion size.

Takayama K *et al* Treatment of severe postmenopausal endometriosis with an aromatase inhibitor. *Fertil. Steril.*

Aromatase inhibitors

- Razzi et al -Treatment of severe recurrent endometriosis with an aromatase inhibitor in a young ovariectomised woman. *BJOG F* 11, 182-184 (2004).

Aromatase inhibitors

- Verma *et al* reported the treatment of three premenopausal patients with refractory endometriosis and chronic pelvic pain with AI. The treatment resulted in a significant reduction in pelvic pain

Verma A, Konje JC: Successful treatment of refractory endometriosis-related chronic pelvic pain with aromatase inhibitors in premenopausal patients. *Eur. J. Obstet. Gynecol. Reprod. Biol.* 143, 112-115 (2009).

Aromatase inhibitors

- Some researchers stated that some form of ovarian suppression needs to be added to the currently available doses of aromatase inhibitors in premenopausal women as estrogen depletion in the hypothalamus may cause FSH secretion and ovarian stimulation if the ovary is not suppressed concomitantly

Aromatase inhibitors

- aromatase inhibitors were administered together with a GnRH agonist, progesterone or a combination oral contraceptive in four phase-II trials - showed a significant benefit

Aromatase inhibitors

- Shippen et al treated two pre-menopausal women with severe endometriosis and pain with **anastrozole combined with progesterone**, calcitriol and rofecoxib
- Treatment resulted in a rapid, progressive elimination of symptoms over 3 months with the maintenance of remission of symptoms for over a year

Shippen ER, West WJ Jr: Successful treatment of severe endometriosis in two premenopausal women with an aromatase inhibitor. *Fertil. Steril.* 81, 1395-1398 (2004)

Aromatase inhibitors

- Amsterdam et al treated fifteen premenopausal patients presenting with documented refractory endometriosis and chronic pelvic pain with **anastrozole in combination with oral contraceptive** for 6 months.
- Significant reduction in pelvic pain scores were noted in 14 of 15 patients and occurred as early as one month after treatment initiation.
 - Amsterdam LL, Gentry W, Jobanputra S, Wolf M, Rubin SD, Bulun SE: Anastrozole and oral contraceptives: a novel treatment for endometriosis. *Fertil Steril* 84(): 300-304 (2005)

Aromatase inhibitors

- Ailawadi *et al* showed laparoscopic evidence of eradicating visible pelvic endometriotic implants and significantly decreasing pain with **letrozole and norethindrone acetate** treatment.
- Ailawadi RK, Jobanputra S, Kataria Meera Gurates B and Bulun SE. Treatment of endometriosis and chronic pelvic pain with letrozole and norethindrone acetate: a pilot study. *Fertil. Steril.* 81, 290-296 (2004).

Aromatase inhibitors

- Soysal et al demonstrated that combination of an **aromatase inhibitor with a GnRH agonist** significantly increased the pain-free interval and decreased symptom recurrence rates.
- Soysal S, Soysal ME, Ozer S, Gul N, Gezgin T: The effects of post-surgical administration of goserelin plus anastrozole compared to goserelin alone in patients with severe endometriosis: a prospective randomized trial. *Hum. Reprod.* 19, 160-167 (2004).

Aromatase inhibitors

- Sasson and Taylor reported the case of a postmenopausal woman with a large, recurrent abdominal wall endometrioma who was successfully treated **with letrozole and medroxyprogesterone acetate**
- Sasson IE, Taylor HS: Aromatase inhibitor for treatment of a recurrent abdominal wall endometrioma in a postmenopausal woman. *Fertil. Steril.* 92, 1170.e-1170.e4 (2009).

Aromatase inhibitors

- Other case reports also suggest that **letrozole either alone or in combination with steroids** is effective in treatment of pelvic pain.
 - Lall et al Aromatase inhibitors in recurrent ovarian endometriomas: report of five cases with literature review. *Fertil. Steril.* 95, 291e15-e18 (2010).
 - Fatemi et al. Successful treatment of an aggressive recurrent post-menopausal endometriosis with an aromatase inhibitor. *Reprod. Biomed. Online* 11, 455-457 (2005).

GnRH antagonists

- GnRH antagonists induce competitive receptor occupancy of GnRH receptor, leading to a rapid and reversible suppression of gonadotropin secretion.
- They have the advantage of having an immediate blocking action on the GnRH receptor without the 'flare-up' effect.

GnRH antagonists

- These drugs are effective in suppressing endometriosis-associated pelvic pain when treatment is continued for 3-6 months
- Kennedy S, Bergqvist A, Chapron C, et al. ESHRE guideline for the diagnosis and treatment of endometriosis. ESHRE Special Interest Group for Endometriosis and Endometrium Guideline Development Group. Hum. Reprod. 20(10), 2698-274 (2005).

GnRH antagonists

- Many Phase I/II and few Phase III studies on the use of oral forms of GnRH antagonists (Elagolix, Abarelix, Cetorelix, Ozarelix, TAK-385) have been done for the treatment of endometriosis-related pain

Selective estrogen receptor modulators

- SERMs are non-steroid molecules that exert selective agonist or antagonist effects in different estrogen target tissues
- SERMs seem to be effective in treatment of endometriosis

Selective estrogen receptor modulators

- However efficiency in pain management? As In a Phase II trial Stratton et al. evaluated whether postoperative treatment with raloxifene was more effective than placebo in women with endometriosis-Women in the raloxifene group experienced more pain and had an earlier second surgery than women in the placebo group leading to an early study termination.
 - Stratton P, Sinaii N, Segars J, et al. Return of chronic pelvic pain from endometriosis after raloxifene treatment: a randomized controlled trial. *Obstet. Gynecol.* 111(1), 88-90 (2008).

Selective progesterone receptor modulators

- They are a class of molecules that act as ligands on the progesterone receptor (PR) ligands.
- They selectively inhibit endometrial proliferation without the systemic effects of estrogen deprivation and induce amenorrhea.
- They bind minimally to ER and have an antiproliferative effect.

Selective progesterone receptor modulators

- They also suppress endometrial prostaglandin production and in this way cause relief of endometriosis-related pain
- Huang HY. Medical treatment of endometriosis. *Chang Gung Med. J.* 31(5), 431-440 (2008).

Antioxidant agents

- Endometriosis is a condition associated with imbalanced oxidative stress.
- Reactive oxygen species (ROS) are up-regulated and antioxidants depleted in the peritoneal fluid of affected women
- Many studies focused on antioxidant agents such melatonin, omega-3 fatty acids, statins and pentoxifylline

Antioxidant agents

- **Melatonin**
- It is an indole mainly produced in the mammalian pineal gland during the dark phase
- It is an important analgesic, antiinflammatory agent, antioxidant, and a free radical scavenger
- It may also have an impact on the extracellular matrix remodeling seen in this disease, through the regulation of the zinc-requiring proteolytic enzymes matrix metalloproteinases (MMPs)

Antioxidant agents

- **Melatonin**

- In a phase II trial Schwertner *et al* investigated the effects of melatonin compared with a placebo on endometriosis-associated chronic pelvic pain (EACPP), brain-derived neurotrophic factor (BDNF) level, and sleep quality.

- Schwertner et al. Efficacy of melatonin in the treatment of endometriosis: A phase II, randomized, double-blind, placebo-controlled trial. *Pain* 154(6), 874-881 (2013).

Antioxidant agents

- **Melatonin**
- They showed that melatonin improved sleep quality, reduced the risk of using an analgesic by 80%, and reduced BDNF levels independently of its effect on pain. This study provided additional evidence regarding the analgesic effects of melatonin on EACPP and melatonin's ability to improve sleep quality.
- It also revealed that melatonin modulates the secretion of BDNF and pain through distinct mechanisms

Antioxidant agents

- **Others**
- A Cochrane database publication recently reviewed four clinical trials on the use of pentoxifylline treatment in women suffering from infertility - the results of this review showed that pentoxifylline was not efficient on pain symptoms and did not improve the chances of spontaneous pregnancies
 - Lu D, Song H, Li Y, Clarke J, Shi G. Pentoxifylline for endometriosis. *Cochrane Database Syst Rev.* 1, CD007677 (2012).

TNF-alpha blockers

- TNF- α is a pro-inflammatory cytokine able to initiate inflammatory cascades.
- Women with endometriosis display increased TNF-alpha (TNF- α) levels in their peritoneal fluid and its levels correlate with the stage of the disease
- There are currently scarce data in humans regarding the use of immunomodulators acting on TNF- α in the treatment of endometriosis.

TNF-alpha blockers

- In a small study of 21 women, Koninckx *et al* studied the effect of infliximab (a monoclonal anti- TNF- α antibody) vs placebo on endometriosis-related pain in women with nodules of deep infiltrating endometriosis and found an improvement of pain symptoms in both the treatment and placebo group - not statistically significant
 - Koninckx PR, Craessaerts M, Timmerman D, et al. Anti-TNF-alpha treatment for deep endometriosis-associated pain: a randomized placebo-controlled trial. *Hum. Reprod.* 23(9), 2017-223 (2008).

Conclusion

- New treatments such as aromatase inhibitors and possible adjuvant therapies were shown to be effective.
- Further studies are necessary to support the clinical use of these novel agents in clinical practice.



Thank you

