

Medical Treatment in Endometriosis

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1. Introduction

Two important targets from medical treatment are: pain control and suppression of disease progress. Most of the time, the effectiveness is temporary and lasted while these drugs have been used, which is expected from the nature of endometriosis disease. Of course, there are some debts about the usefulness of pain relief agents, because 30-50% of patients feel better with placebo administration.

It must to keep in mind that those common administrated drugs couldn't help to restore the fertility potentials and in fact during their usage pregnancy cannot or should not be happened, regarding to inhibition of ovulation or teratogenic effects; of course by their administration with remission of disease (suppress the growth and activity of previous endometriotic implants) and reducing the chance of new peritoneal seeding, fertility may be preserved better; but at the end for achieving pregnancy other ways should be used.

Medical therapeutic drugs divided in two categories:

- a. Non hormonal medical therapy.
- b. Hormonal medical therapy.

Non hormonal therapeutic options, mainly work on inflammatory and immunologic aspect of endometriosis and hormonal attempts basically deprived endometriotic implants from their nutritive substance: estrogen.

2. Non hormonal medical therapy

2.1 Non-steroidal anti- inflammatory agents

With attention to inflammatory nature of endometriosis, for decades non- steroidal anti-inflammatory agents (NSAIDs) such as naproxen and ibuprofen have been administrated for pain control, in endometriosis. These drugs have been reduced prostaglandins (PGs) production, the main stimulator factor in peritoneal nerves and decrease the nociceptor input messenger from the peritoneal endometriotic implants into central nervous system. Their gastrointestinal upsets and inhibition of ovulation (Duffy &Stouffer,2002) against low cost and easy availability, always puts NSAIDs in a challenging situation; rather than, new NSAIDs as a selective cyclooxygenase (COX)-2 inhibitors like celecoxib without any effect on PG pathway, could induce apoptosis in endometriotic implants (Seo etal,2010). However

the latest Cochrane review doesn't show significant effective role of these drugs in patients with endometriosis (Davis et al, 2007).

2.2 Cytokines inhibitors

Research in this field is still in primary stages. In animal experiments, cytokines antagonist agents like recombinant human tumor necrotizing factor alpha (TNF- α) binding protein could inhibit the progress of endometriotic implants and formation of their adhesion (Barrier et al,2004;D'Hooghe et al,2006). Etanercept (ETA) as a TNF antagonist could decrease the volume of peritoneal fluid and proliferation of lesions in endometriotic rats (Zulfikaroglu et al,2011). In a novel study, has been found that TNF could activate estrogen receptor α (ER α); therefore co-administration of a pure ER antagonist with TNF inhibitor could be a more efficacious therapeutic method than usage of one agent, separately (Gori et al,2011).

2.3 New anti inflammatores

In cases with persistent non responsive symptom to NSAIDs, other inflammatores like leukotrienes could be inhibited (Abu et al, 2000). In one new study, leukotriene receptor antagonist has been shown to have a significant effect in reduction of stromal proliferation in endometriotic implants (Ihara et al, 2004).

2.4 Immuno modulators

Pentoxiphylline administration in human, like a leukotriene receptor antagonist, had promising results in patients with endometriosis. Although it is famous as a vasodilator agent and increase tissue oxygenation in some disease; but could change the immune cell function by inhibition of cytokine and TNF- α secretion. Although in a Cochran review in year 2009, there were not shown enough evidence to support any differences in pregnancy rate in treated patients in comparison with placebo (Lu et al,2009); but in a new report, Vascular endothelial growth factor (VEGF)-C suggested to be an effective factor for significant reduction in endometriotic implants after Pentoxiphylline administration (Vlahos et al,2010).

Also, other immuno modulators like etanercept (ETA) had promising reductive effect equally to letrozole in early investigation (Ceyhan et al ,2011).

2.5 Alternative medicine

In a 16 weeks prospective clinical trial, Chinese herbal medicine (CHM) decoctions have been disclosed hopeful reduction in patient's symptoms especially with dysmenorrhea complaint rather than placebo (Flower et al, 2011). According to Cochrane review, CHM have been shown equal results in comparison with gestrinone with lesser side effects; beside that, the combination of oral CMH administration with a CMH enema appear better clinical outcomes (Flower et al, 2009).

As well, there are some published studies about the effectiveness of acupuncture in abdominal pain and significantly in dysmenorrhea relief (M.Chen et al ,2010 ; Rubi-Klein et al,2010). In another clinical trial, abdominal acupuncture causing decrease in CA125 level in endometriotic patients (Xiang et al, 2011).

3. Hormonal medical therapy

3.1 Oral contraceptive pill (OCP)

Oral combined contraceptive pills induce atrophy in peritoneal endometriotic implants by initial decidualization effect like a pseudo pregnancy situation; perhaps they could increase the apoptosis in endometriotic implants (Meresman et al, 2000). OCPs are the most prescribed drugs in endometriosis, especially in minimal and mild stages of disease for pain control ; although there is a new report about the effectiveness of OCPs usage in patients with deep endometriotic nodules (advance stage) (Mabrouk et al,2011) ,which eliminate the effectiveness of OCPs administration only in early stages of disease. In addition, there is not any differences between various available formulations in pain relief potency and any kind of OCPs which had 30-35µg of ethinyl estradiol could be used and there is no necessity for high dose (HD) contraceptive administration (with 50 µg of ethinyl estradiol) (Davis et al,2007) . About the usage methods has been shown that, continues usage had better clinical results rather than cyclic administration (Harada et al,2008). In cases of sever atrophy of endometrium and break through bleeding, supplemental estrogen for 7-10 days could be advised.

3.2 Progestins

Progestins at the first stage of administration induce decidualization in endometriotic tissues and at the second phase by proliferation inhibition makes atrophia. Also, progestins make depletion in estrogen receptors and inhibit their activation (Kirkland et al, 1992). Progestins could induce transformation of potent form of estrogens (estradiol) to weaker product (estrone) (Tseng et al, 1981) .In recent studies discover that there are two important catalyzer enzymes which metabolize progesterone in endometriotic implants. Aldo-Keto reductase 1C1 and 1C3 (AKR1C1 & AKR1C3) had significant up-regulation expression in ovarian endometriosis which interfere with inhibitory effects of human progesterone (Hevir et al, 2011). It found that exogenous progestins administration could inhibit their activity (Beranic et al, 2011). Various available progestins could be used: oral, parenteral, intrauterine device and implants. With higher dosage of administrated progestins, another effective role of them could be achieved: inhibition of matrix metalloproteinase (Osteen et al , 2003). Most of the time the clinical response to progestins are like the oral contraceptive pills (Schlaff et al,2006), without significant side effects except breakthrough bleeding which can be managed with short time, low dose estrogen administration. Also, the probably bone loss effect is reversible (Cundy et al,1996).The levonorgestrel releasing intrauterine device (LNG-IUS) is a valuable therapeutic option especially for women with deep infiltrative endometriotic implants (Lochat et al,2005).About the pain relief efficacy of progestin subdermal implants (Implanon) evidences are limited than other therapeutic modalities (Yisa et al,2005).

3.3 Gonadotropin-releasing hormone agonists

Gonadotropin -releasing hormone (GnRH) agonists are synthetic drugs which are resistant to degeneration in body and are produced by some variation in amino acids consequent in natural GnRH agonists. Their resistance to degeneration makes the pituitary gland into

down regulation state and after suppression of FSH and LH production, menstruation and ovulation had been stopped and therefore, low estrogenic environment achieved which inhibits the proliferation in endometriotic implants. Beside initial flare effect, pseudo menopausal situation produce minor side effects like hot flashes, vaginal atrophica and dryness, headache and other vasomotor signs and symptoms (Dlugi et al,1990) which could be managed by add-back therapy, but after 6 or more continues cycles of drug administration, bone mineral density is going to be reduced sometimes in an irreversible manner (Taga et al,1996); but there is an interesting report about ten years usage of GnRH agonist with add-back therapy without any bone mineral loss (Bedaiwy et al,2006). Unlike the progestins and danazole, GnRH agonists had not adverse effects on lipid profile (Burry et al,1989).Several kinds of injectable GnRH agonists and nasal spray form are available with equal efficacy (Prentice et al,2000).

3.4 Gonadotropin-releasing hormone antagonists

Regarding to initial flare effect of GnRH agonist administration and probably exacerbation effect on endometriosis and a delay between their administration and real hypo estrogenic state and their intolerable side effects in some patients, GnRH antagonists became an suitable substitute for GnRH agonists. Weekly subcutaneous 3-mg cetrotide (GnRH antagonist) injection had been shown clinical efficacy without pseudo menopausal side effects (Finas et al, 2006; Kupker et al, 2002). There are some published advances in oral GnRH antagonist production: Elagolix (C.Chen et al, 2008). In a double blind study in 55 patients, weekly usage of this drug , results effective suppression of gonadal hormonal production (Struthers et al,2009), which could be a promising development in endometriosis treatments modalities instated of injectable options.

3.5 Androgens

Danazol is a derivation from testosterone which effect on endometriosis from several ways. Danazol inhibit some steroidogenic enzymes and elevate free testosterone and reduce estrogen level (Barbieri et al, 1981). Also, danazol inhibit mid cycle LH surge (Tamura et al, 1991) and PG F₂ α production in ovary (Kogo et al,1992),which both of them result chronic anovulation and decrease the chance of new peritoneal seeding.Danazol with 400-800 mg/ daily recommended dosage regress the endometriotic implants (Telimaa et al,1987), but severe side effects prevent such dosage administration for an effective period (6 months) (Miller et al,1998).Oily skin, acne, hirsutism, irreversible voice deepness, variation in lipid profile, vaginal atrophica and hot flash limited it's prescription (Hayashi et al,2001).

3.6 Aromatase inhibitors

In opposition to other hormonal therapeutic options which reduce ovarian estrogenic production, aromatase inhibitors act not only locally on endometriotic implants, but also on all of estrogenic producers: ovary, brain, adipose tissues (Attar&Bulun, 2006). Anastrozole 1mg or letrozole 2.5mg daily could be effective in pain relief associated with endometriosis (Nothnick, 2011; Shippen&West, 2004). Because of stimulatory action of aromatase inhibitors in FSH secretion, in premenopausal women they could cause ovarian cysts;

therefore they administrate with GnRH agonist or OCPs or progestins. This method could reduce the concern about their disadvantage in prolong usage: bone loss (Ferrero et al, 2009).

3.7 Prolactin secretion inhibitors

Suppression of cellular immunity and NK cell activity in endometriotic patients has been well known. Also, in stressful situations inhibition of NK cell had been found (Chrousos et al, 2000). Prolactin and cortisol levels in serum are stress indicators. Of course the mechanism of hyper prolactinemia in response to stress isn't so clear, elevated level of serum prolactin had been found in endometriosis like other stressful conditions (Lima et al, 2006, Wang et al, 2009). Interestingly the mean serum prolactin levels are higher in advance stages in endometriotic patients (Gregoriou et al, 1999). Quinagolide as a dopamine receptor 2 agonist by reduction in VEGF receptor (a main factor for angiogenesis) could decrease the size of peritoneal lesions and in some cases could eradicate all of endometriotic implants (Gomez et al, 2011). From another aspect quinagolide, is a valuable option for hyper prolactinemia like other dopamine agonists (bromocriptine or cabergoline) (Barlier & Jaquet, 2006); therefore this drug could be effectively administrated in endometriosis.

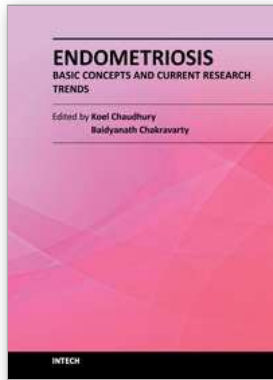
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This book provides an insight into the emerging trends in pathogenesis, diagnosis and management of endometriosis. Key features of the book include overviews of endometriosis; endometrial angiogenesis, stem cells involvement, immunological and hormonal aspects related to the disease pathogenesis; recent research reports on infertility, endometrial receptivity, ovarian cancer and altered gene expression associated with endometriosis; various predictive markers, and imaging modalities including MRI and ultrasound for efficient diagnosis; as well as current non-hormonal and hormonal treatment strategies This book is expected to be a valuable resource for clinicians, scientists and students who would like to have an improved understanding of endometriosis and also appreciate recent research trends associated with this disease.

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