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Medical management of endometriosis

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Abstract

Endometriosis is a chronic and benign gynecological disorder affecting women of reproductive age group. This chronic disease has a negative impact on the quality of life of women by causing symptoms like chronic pelvic pain, severe dysmenorrhoea, dyspareunia and infertility. Given a 10%-20% prevalence rate among women of reproductive age, it contributes to more than 100,000 hysterectomies worldwide each year. Although a number of medical managements are available at present but most of these produces adverse effects like induction of a hypo-estrogenic state, which further enhances infertility and unwanted menopausal-like side effects. Furthermore, recurrence of symptoms is common during treatment-free intervals. These major drawbacks of current treatments often lead to abandonment of medical therapy and calls for repeated surgical therapy. Present review article is an evaluation of currently available options and advances in medical interventions.

Keywords: Endometriosis, Treatment, Medical management, new modalities.

1. Introduction

Endometriosis is a chronic and benign gynecological disorder affecting women of reproductive age group. It is characterized by the presence of endometrial gland and stromal tissue outside the uterine cavity, primarily within pelvic cavity. This chronic disease has a negative impact on the quality of life of women by causing symptoms like chronic pelvic pain, severe dysmenorrhoea, dyspareunia and infertility. Given a 10%-20% prevalence rate among women of reproductive age, it contributes to more than 100,000 hysterectomies worldwide each year [1]. Over the past few decades, the incidence of endometriosis in women presenting with chronic pelvic pain and infertility has been reported to be as high as 80% [2].

At present there are insufficient treatments for the disease. Current medical treatment regimes rely on the fact that endometriosis is an estrogen-dependent disease and are limited to hormonal drugs that suppress the menstrual cycle and activity of endometriotic lesions, aiming to relieve pain and bleeding. Yet, relief is at the cost of adverse effects of these drugs like induction of a hypo-estrogenic state, which further enhances infertility and unwanted menopausal-like side effects. Furthermore, recurrence of symptoms is common during treatment-free intervals. These major drawbacks of current treatments often lead to abandonment of medical therapy and calls for repeated surgical therapy.

As a result, focus remains on identification of novel targets for endometriosis treatment. Treatments that directly target the endometriotic implant would minimize the systemic adverse effects typical of traditional treatment modalities. However, currently there are no endometriotic implant specific treatment options that have been successful. With improvement of our understanding of the pathophysiology behind endometriosis, advances in medical intervention have been made possible with varying degrees of success.

2. Conventional treatment modalities

In current scenario endometriosis is being managed medically with the following therapeutic agents: gonadotropin releasing hormone (GnRH) agonists, progestins, OCP's and danazol. As the disease is chronic and recurrence is common, long-term or repeated courses of treatment is often required.

2.1 Gonadotropin-releasing hormone agonists

Gonadotropin-releasing hormone agonists are effective in relieving pain associated with endometriosis [3]. Upon administration, initially there is an increase in gonadotropins; subsequently, a down regulation resulting in decreased estrogen production. The result is the adverse hypoestrogenic side effects most important being loss of bone mineral density and suppression of ovulation, which further enhances infertility. Other symptoms include vasomotor symptoms, atrophic vagina, insomnia, mood disorders, and cognitive dysfunction. Patients are initially started on a 3 to 6-month course of these drugs. Clinical trials have shown that the majority of patients respond with pain relief; however, recurrence of pain is common as well. To reduce the adverse effects, add-back therapy has been introduced in conjunction with GnRH agonist administration [4]. The most commonly used add-back regimens include norethindrone and low dose estrogen.

2.2 Progestins

Progestin provides an alternate therapeutic approach for endometriosis-associated pain. Subcutaneous medroxyprogesterone acetate (Depo-SubQ-Provera 104) is administered every 12 to 14 weeks to relieve pain symptoms [5]. Ovulation is thereby suppressed which is efficacious in managing chronic pain but compromises fertility. As with GnRH agonists, the primary concern with progestin use is the potential loss of BMD. Although the efficacy of both treatment regimens is comparable in relieving pain symptoms, studies have shown that GnRH agonists have persistent as well as higher degree of BMD loss. Prolonged use of Depo-SubQ-Provera 104 is not recommended.

2.3 LNG – IUD

The LNG-IUD is an effective hormonal option for treating symptomatic endometriosis.

LNG IUD delivers significant amounts of levonorgestrel into the peritoneal fluid, clearing up the local effect on the endometriotic tissue by inducing decidualization. For long-term treatment, the LNG-IUD may be a treatment of choice, since it permits the same system to be used for at least 5 years with no modifications in estrogen levels and few hypoestrogenic side effects; making it cost effective and more effective than other progestins[6].

2.4 OCP's

Combined hormonal contraceptives have been used in both a cyclic and a continuous manner in the treatment of endometriosis. They inhibit the production of estrogen by a negative feedback mechanism. They also lead to a reduction in estrogen-induced production of prostaglandins, thereby decreasing the inflammation associated with endometriosis. Combined OCs containing the new generation progestogen- desogestrel, gestodene have proven to be more effective than COC's containing 19 nortestosterone derivatives. Continous OCP's have been found to be more effective than cyclical regime [7]. However there is fast recovery of the disease once the treatment is interrupted. Also another major risk includes the increased risk of thromboembolic events.

2.5 Danazol

A 17-ethinyl-testosterone derivative, danazol has similar efficacy to GnRH agonists in relieving chronic pain symptoms associated with endometriosis. The adverse effects differ and are associated with the androgen properties like weight gain, edema, acne, hirsutism, myalgia, altered lipid profile and deranged liver enzymes. Danazol further suppresses LH and FSH, thus, inducing amenorrhea and enhancing infertility. During the 6-month danazol treatment, it has been seen that recurrence of pain symptoms occurs with the same frequency as with GnRH agonists. The combination of adverse side effects and recurrence of pain makes this agent less tolerated amongst patients, and compliance is low.

3. New treatment modalities

3.1 Dienogest – a novel progestin for long term treatment of endometriosis

Dienogest is a new synthetic oral progestin having strong progestational and moderate antigonadotrophic effects, but no androgenic, glucocorticoid or mineralocorticoid activity. Dienogest reduces endometriotic lesions through a number of biological mechanisms including reduction in expression of inflammatory factors. It inhibits key enzymes in the metabolism of estrogens, leading to modest reduction in endogenous production of estradiol and thus exerting a therapeutical effect in endometriosis**.** It has high oral bioavailability and a half life suitable for once-daily administration, a dose of 2mg/day moderately suppresses estrogen levels.

Various studies have shown that dienogest has a favourable safety and tolerability profile, with predictable adverse effects, high rates of patient compliance, and low withdrawal rates.

Dienogest is a progestin investigated for the treatment of endometriosis. Dienogest at a dose of 2 mg daily has been studied extensively in clinical trial programs performed in Europe and Japan, including two studies with treatment durations of up to 65 weeks. These studies demonstrated that dienogest has an efficacy, safety, and tolerability profile that is favorable for long-term use. The intensity of pain associated with endometriosis decreased progressively, adverse events (mostly mild or moderate in intensity) were predictable and associated with low is continuation rates, and bleeding irregularities reduce Dienogest is a progestin investigated for the treatment of

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Dienogest use was however associated with a higher incidence of abnormal menstrual bleeding patterns, although this was generally well tolerated by patients. Studies have also shown that dienogest is as effective as surgical treatment in relieving pain in more than 90% of women with deep infiltrating endometriosis (DIE) at one year follow-up [9]. There are a few pilot studies describing the efficacy of dienogest on extra genital endometriosis like in cases with colon and bladder endometriosis [10].

3.2 Aromatase inhibitors

Endometriosis is an estrogen dependent condition and there is increased expression of aromatase P450 in the endometriotic tissue. This forms the physiologic basis for the treatment of endometriosis with aromatase inhibitors. Aromatase P450 converts androstenedione and testosterone to estrone and estradiol respectively, thus inhibition of this enzyme reduces local estrogen production. Anastrozole and letrozole, both third-generation agents competitively bind to the heme group of the cytochrome P450 subunit, resulting in inhibition of aromatase. As the estrogen level decreases, there is an increase in FSH and LH which directly stimulates the ovary. Therefore, using an AI not only help in alleviating the pain associated with endometriosis, but can also treat the infertility aspect when used for ovulation induction and in IVF protocols. Clinical trials have shown that aromatase inhibitors are effective in treating patients with endometriosis refractory to conventional medical and surgical options. Observational studies have reported that AIs combined with either progestogens or oral contraceptive pill reduce the severity of pain symptoms, have lower discontinuation rate than GnRh agonists and improves the quality of life [11].

3.3 Antiangiogenic agents

Ectopic endometrial tissue needs to establish blood supply in order to thrive outside the uterine cavity. Elevated levels of VEGF-A in peritoneal fluid has been found in women with endometriosis. VEGF-A is a potent stimulator of angiogenesis. It signals migration, proliferation and differentiation of endothelial cells that initiates the neovascularization from existing blood vessels. Till date studies on mouse model only have reported efficacy of antiangiogenenics to treat endometriosis [12].

3.4 Immunomodulators

It has been seen that altered immune function plays a crucial role in the pathogenesis and pathophysiology of endometriosis. Based on this, several investigators suggested that modulating the inflammation through immune-modulators could be an alternative approach for treatment of endometriosis. Till date there are no large scale human trials, but initial studies in rodent models are promising. It includes loxoribine, IFN-α2b and TNF-α inhibitors.

Loxoribine stimulates natural killer cells, which then do not allow endometrial cells to implant in ectopic tissues. Only one small study in rat models showed that there was a significant reduction in amount of disease, further studies are under observation.

IFN- α2b have been shown to decrease endometriosis in animal models and in tissue cultures. The route of administration is invasive, either by intraperitoneal placement during laparoscopy or by subcutaneous injections.

Elevated levels of TNF-α has been found in the peritoneal fluid, peripheral blood, and endometrial tissue of women with endometriosis as compared to women without endometriosis. TNF-α plays an important role in the inflammatory cascade by inducing expression of IL-8 and RANTES, which in turn recruit T cells, macrophages, and eosinophils. It up regulates the expression of matrix metalloproteinases and other inflammatory cytokines, necessary for endometriotic tissue invasion and angiogenesis [13]. The level of TNF-α varies with the severity of the disease. Studies have found anti-TNF-α agents effective in reducing lesion size, specifically red lesion size; however their effect on established lesions is not as promising. To date, only one human trial involving 21 participants has been done. Results showed no evidence of improvement of pain score after treating by infliximab, one of the known anti-TNF-α drugs.

Pentoxifylline, a phosphodiesterase inhibitor, inhibits phagocytosis and generation of toxic oxygen species and proteolytic enzymes by macrophages and granulocytes in vitro and in vivo. A Cochrane review to determine the effectiveness of pentoxifylline, in the management of endometriosis in subfertile women showed that pentoxifylline had neither significant effect on reduction of pain nor increase in fertility rate [14]. Further studies are required for establishing its role in endometriosis.

3.5 Selective progesterone receptor modulators (SPRM)

SPRM are progesterone receptor ligands that exhibit agonist/antagonist effects based on the target tissue, dose and presence or absence of progesterone. They can induce reversible amenorrhea through selective inhibition of endometrial proliferation. They have a direct effect on endometrial blood vessels and the potential to suppress endometrial prostaglandin production in a tissue-specific manner without the systemic effects of estrogen deprivation, providing a rationale for the treatment of endometriosis-related pain. Asoprisnil is the first SPRM which has reached an advanced stage of clinical development for the treatment of endometriosis [15]. It can suppress both the menstrual cycle and endometrial growth. To date, there is only one published clinical trial establishing the role of asoprisnil in decreasing pelvic pain associated with endometriosis.

Currently various studies, mainly on animal models are being done to find novel drugs in the treatment of endometriosis which are free of side effects of traditional modalities like hypoestroegenic effects and infertility. Various agents like 5fluorouracil, thiazolidinediones, doxcycline, SERMS, MMPs and many more are under clinical trials. A wider range of such medical options allows for the possibility of a more tailored treatment approach for women with endometriosis.

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