Current and future medical treatment of adenomyosis

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Adenomyosis is a benign gynecological disorder associated with abnormal uterine bleeding (AUB), dysmenorrhea, dyspareunia and infertility and requires a life-long management plan including medical and surgical treatment. The choice depends on the woman’s age, reproductive and gynaecological status and clinical symptoms. Medical treatment has a priority in patients that require preservation of fertility and improvement of quality of life and several studies are focusing on medical treatment for adenomyosis.

Following the pathogenetic data, adenomyosis is a sex hormone related disorder and the most common drugs modulate estrogen/progesterone receptors. A main target is to block the hypothalamic-pituitary-gonadal axis using GnRH agonist. However, the use of GnRH agonists for long term is associated with frequent and intolerable hypoestrogenic side effects, including vasomotor syndrome, genital atrophy, and mood instability; it also has a negative impact on bone health and on cardiovascular health. Aromatase inhibitors (AIs) also produce a hypoestrogenic environment and have been proposed for adenomyosis-related pain, but are correlated with high incidence of adverse effects and a recurrence of symptoms after discontinuation of treatment.

An antiproliferative effect of progestins suggests their use for treating adenomyosis. Continuous oral/vaginal norethisterone acetate or subcutaneous depot medroxyprogesterone may help to inducing regression of adenomyosis, relief pain and reduce bleeding. Vaginal danazol has therapeutic effect on adenomyosis by a direct interaction with endometrial receptors for androgen/progesterone reducing pain and AUB. The intrauterine device releasing levonorgestrel (Lng-IUD) has been widely assessed in AUB, resulting extremely effective in resolving also pain associated with adenomyosis. Side-effects are characterized mainly by irregular bleeding and amenorrhoea. Under development are some selective progesterone receptor modulators (SPRMs), which reduce adenomyosis- associated pelvic pain, inhibit endometrial proliferation and suppress adenomyotic lesions, resulting in inhibition of prostaglandin production and endometrial atrophy in animal models. Clinical studies with SPRMs are currently done.

New therapeutic target useful for the development of new long-term therapies are under investigation. Inflammatory genes are increased in eutopic endometrial tissue and in adenomyosis, like cyclooxygenase-2 (PLAG2) and corticotropin-releasing hormone, and drugs inhibiting prostaglandins synthesis or receptors are for the treatment of adenomyosis. Adenomyotic nodules show high nerve growth factors-mRNA and myostatin, which causes proliferation, apoptosis and angiogenesis and new molecules modulating these genes are under investigated in order to combined hormonal and non-hormonal drugs for targets multiple site of action.