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Conservative treatment of genital endometriosis forms

Hana Hrušková
Department of Obstetrics and Gynecology, First Faculty of Medicine of Charles University in Prague and General University Hospital, Czech Republic

Correspondence: MUDr. Hana Hrušková, Gynekologicko-porodnická klinika 1. LF UK a VFN, Apolinářská 18, Praha 2, 128 51, Czech Republic, tel.: +420 224 967 118, e-mail: hahruskova@seznam.cz

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Review article

Abstract
The article gives a brief overview of the possibilities of conservative treatment of endometriosis. Taking as a basis the known pathophysiology of the disease, this involves hormonal treatment – not just of the kinds currently used, such as combined hormonal contraceptives, progestins or gonadotrophin analogues, but also a method which has undergone clinical studies but is rarely used today due to its cost or significant adverse effects. The article also mentions the analgesic and alternative treatment which extends the therapeutic options for endometriosis and helps remove its main symptom: pain.

Key words: endometriosis, hormonal treatment of endometriosis, NSAIDs in the treatment of endometriosis

KONZERVATIVNÍ LÉČBA GENITÁLNÍCH FOREM ENDOMETRIÓZY

Přehledový článek

Abstrakt
Článek podává stručný přehled o možnostech konzervativní léčby endometriózy. Na základě poznané patofyziologie nemoci představuje léčbu hormonální, a to nejen aktuálně používanou, jako je kombinovaná hormonální antikoncepce, progestiny nebo analoga gonadoliberinů, ale i tu, která prošla klinickými studiemi, ale z důvodu ekonomické náročnosti nebo výrazných nežádoucích účinků se dnes používá jen výjimečně. Článek zmiňuje i léčbu analgetickou a alternativní, která rozšiřuje terapeutické možnosti léčby endometriózy a pomáhá odstranit její hlavní symptom, a to bolest.

Klíčová slova: endometrióza, hormonální léčba endometriózy, NSAID v léčbě endometriózy

Introduction
Endometriosis (ETRS) is an estrogen–dependant, inflammatory systemic and chronic disease characterized by the presence of a functional lining of the uterus outside the uterine cavity. It is a fairly widespread condition affecting approximately 5% – 10% of women in reproductive age (1). Typical symptoms include recurrent episodes of dysmenorrhea, dyspareunia and pelvic pain, as well as infertility.

Treatment strategies for endometriosis
The aim of the treatment of endometriosis is to mitigate the pain and improve the quality of life of the women affected. Various pharmaceuticals are used in therapy, often in combination. So far there is no common therapeutic approach that could be used for all patients, and treatment of endometriosis is always on case-by-case basis, considering clinical symptoms, as well as the age and parity of the patient, and the findings of laparoscopy (if carried out). Moreover, we aim for holistic treatment, combining conservative and surgical approach, in a neoadjuvant (applying pharmacotherapy before the surgical treatment) or adjuvant (surgical treatment of deposits, with subsequent hormonal suppression of ovulation) therapeutic regime. Nevertheless, the recurrence rate of the disease is high, as much as 70% (2).

Tab. 1 *Basic scheme of treatment of endometriosis*

Pathophysiological cause of ETRS	**Aim of the therapy**	**Reason**	**Treatment**
Excessive production of estradiol	Suppressing estrogen secretion	Suppressing the growth of endometrium	Natural pregnancy, pseudo- gravidity, pseudo-climacterium
Insufficient inactivation of estradiol to estrone	Influencing aromatase	Participates in synthesis of estrogens	Inhibition of aromatase
Resistance to progesterone	Influencing progesterone receptor	Has anti-estrogen effect on endometrium	Increasing sensitivity, increasing the number of progesterone receptors
Excessive creation of prostaglandins	Influencing cyclooxygenase (COX-2)	Participates in synthesis of prostaglandins	Blocking the synthesis of prostaglandins

Pharmaceutical treatment of endometriosis
Endometriosis is a hormone-dependant disease; therefore the primary treatment should always be hormonal. Pharmacotherapy has 4 basic directions, based on the known pathophysiology of the disease.
Tab. 1 shows that in the pharmaceutical treatment of endometriosis we aim to suppress the cyclical ovarian secretion of estrogens in women, either by natural pregnancy, pseudo-gravidity (by applying combined oral contraceptives), or by inducing a hypoestrin condition: climacterium. Another possibility involves trying to affect the progesterone receptor, influencing aromatase, which takes part in the biosynthesis of estrogen, and cyklooxygenase, which is a component in the synthesis of prostaglandins.

Hormonal treatment
Combined oral contraceptives (COC)
The use of combined hormonal contraceptives, i.e. estrogene–gestagene preparations, is the basis of pharmaceutical treatment of endometriosis. If pain is the dominating symptom, and the patient is not trying for pregnancy, COC may be applied empirically, without laparoscopy diagnostic. By inducing pseudo-gravidity with decidualisation of the endometrium, we achieve relief from the symptoms (mitigation of dysmenorrhea and pelipathia) for 60% – 90% of patients (3). For this purpose we prefer monophasic preparations with a strong gestagen component, which have a powerful effect on the endometrium and lack the androgenic and mineralocorticoid effect. We use advanced, low-dosage contraceptives, and to limit the clinical symptoms, we recommend continuous treatment in a so-called long cycle.

Progestins
Progestins are often the first-choice drug due to the low cost and variety in forms of application, and they have been used in the treatment of endometriosis for decades, based on clinical experience. They cause atrophy of the endometrium after initial decidualisation. Vercellini et al. reviewed data from four randomized studies with progestins in the treatment of endometriosis and determined that the effect of progestin in providing temporary relief from endometriosis-associated pelvic pain, EAPP is good and comparable with other, less safe preparations (4).
The only progestin for which systematic research has been carried out in a comprehensive programme of clinical assessments dealing with therapy of endometriosis is dienogest. Dienogest uniquely combines the pharma-

ceutical advantages of 19-norprogestins and progesterone derivatives. It has a considerable effect on the endometrium, combined with a low affinity to estrogen, androgen, glucocorticoid and mineralocorticoid receptors. Depot medroxyprogesterone acetate (MPA) at a dosage of 104 mg or 150 mg, applied every 90 days for a period of 12 months, showed the same effect in mitigating the symptoms of endometriosis as danazol or GnRH antagonists (5,6).
However, a possible negative effect on bone density associated with its long-term use has been established. Furthermore, the time delay in restarting ovulation after termination of the therapy is a contraindication for women who wish to become pregnant in the near future (7,8).
Depot levonorgestrel (LNG), which is a part of the intrauterine system, works locally in the uterine cavity in high concentrations, inducing atrophy of the epithelial cells and decidualisation of the stromal cells of the endometrium. Although the exposure to the hormone in the uterine cavity is high, the concentration gradient from endometrium to myometrium is considerable (gradient endometrium/myometrium approximately 100 times lower) and concentrations of LNG in the serum are very low (gradient endometrium/serum approximately 1000 times lower). Despite this, a number of studies have confirmed a positive effect of IUS-LNG on dysmenorrhea and dyspareunia in patients suffering from endometriosis (9).

GnRH analogues
The principle of the treatment is inducing a hypoestrin condition: pseudo-climacterium. It involves synthetic decapeptil analogues of natural gonadotropin–releasing hormone (GnRH). Studies have shown that after an initial stimulation (flare–up effect), prolonged application of analogues suppresses the secretion of the body's own gonadotropin, with subsequent inhibition of ovarian functions. Additionally, a direct effect on the gonads has been proven, reducing the sensitivity of peripheral receptors to GnRH. Long-term treatment reduces levels of FSH (follicle-stimulating hormone) and LH (luteinising hormone) to the level of steroid castration within 2–3 weeks from starting the application, with the effect lasting throughout the application. Analogues include buserelin, goserelin, leuprorelin, nafarelin, tripto-relin, histrelin, deslorelin. The application form is intramuscular, intranasal or subcutaneous. The effect of the analogues is good: 50% – 90% of patients felt relief from pelvic pain, dysmenorrhea and dyspareunia. Also, the effect appears more quickly than in other, mainly per oral application forms. However, application of analogues has considerable adverse effects: acute climacteric syndrome from the induced sudden hypoestrin condition, and a negative effect on bone density (bone loss of 4% – 6% after a 6 month course); for this reason the treatment is limited to a maximum of 6 months of application, as after this time the bone can still return to normal within 6–12 months after termination of the therapy. Strong vegetative symptoms of the climacteric syndrome can be mitigated by "add-back" therapy (application of hormone replacement therapy) which will not affect the desired suppression of ETRS deposits.

Danazol
This is a highly effective preparation mitigating the symptoms of endometriosis; however, numerous adverse affects limit its use. It is an androgenic steroid that inhibits LH and FSH, with the effect of inducing a relative hypoestrin condition and atrophy of endometrium. This makes it effective in the treatment of the symptoms of endometriosis, though its use is limited by its characteristic side effects on the metabolism of lipids and adverse effects such as weight gain, edema, acne, vaginal dryness, flushing, increased skin greasiness, hirsutism and liver toxicity (10,11). For these reasons, danazol has been replaced in many countries by newer preparations for the treatment of endometriosis.

Gestrinon
A derivative of 19–nortestosteron, gestrinon is one of the anti-gonadotropin group and has a weak androgenic activity. Application of gestrinon causes degeneration and inactivation of deposits of endometriosis by inducing a secondary amenorrhea. Adverse effects of the therapy are similar to those of danazol (involving signs of increased androgenic activity), so gestrinon is rarely used in the management of ETRS.

GnRH antagonists
GnRH antagonists compete with natural GnRH for binding to GnRH receptors in hypofyse (competitive blocking), and after binding with the receptor they have the immediate effect of reducing the secretion of gonadotropin (without the flare-up effect), and subsequently the levels of sexual hormones. Substances referred to as antagonists of the first and second generation (Detirelix, Nal-Glu), while being able to effectively suppress secretion of gonadotropin, have local and systemic allergic reactions. Histamin released from mastocytes causes local erythema, even a systemic reaction with a drop in blood pressure. These preparations are thus not usable in clinical practice (12,13). Only the third generation of antagonists brought drugs with high effect and no adverse effects (Ganirelix, Cetrorelix). However, treatment of endometriosis by GnRH antagonists has so far been only carried out within a few studies; their introduction in practice is currently limited by cost and semi-depot application, which renders long-term therapy impossible. Therefore the main indication for use of GnRh antagonists is an effective inhibition of undesired early secretion of LH in ovarian stimulation in connection with treatment of primary sterility.

Progestin antagonists and selective progesterone receptor modulators
It is appropriate to at least mention this treatment method, as it is frequently referred to in connection with therapy of endometriosis, although it is not yet used in clinical practice and is still in the stage of experimental studies. Progestin antagonists and selective modulators of progesterone receptors have an anti-proliferative effect on endometrium without the risks of hypoestrin condition. Mifepriston, discovered in the laboratories of the French firm Roussel Uclaf in 1980 during research into glucocorticoids, made it furthest in the market. Clinical tests started in 1982, and it is remembered in medical

circles mostly for its abortive effect. It has not been registered in the Czech Republic. A clinical study on treatment of endometriosis proved approximately 50% curative effect on pelvic pain and dysmenorrhea (14).

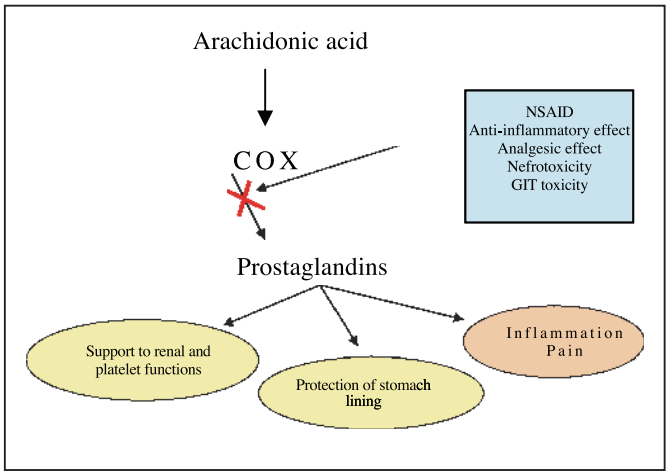
Selective estrogen receptor modulators of (SERM)
These substances of a non-steroid character activate or inhibit estrogen receptor and compete for binding with the endogenous estrogen. Their effect varies, depending on the quantity and distribution of estrogen receptors in the target tissue. An ideal selective estrogen receptor modulator would preserve the estrogenic effect on bones, the central neural system and the cardiovascular apparatus, while having anti-estrogenic effects on breasts and gonads.
So far no such substance is available for clinical use. Most clinical experience has been gained with tamoxifen, which is indicated for adjuvant treatment of breast carcinoma. Due to its stimulating effect on endometrium it is unsuitable for treating endometriosis.
Another of the SERM substances is raloxifen, indicated for the treatment and prevention of post-menopausal osteoporosis. Unlike tamoxifen, raloxifen does not cause stimulation of endometrium, and its use is not connected with an increased risk of vaginal bleeding, endometrial hyperplasia or endometrial carcinoma (15). However, it is only intended for menopausal women, so its indication for treatment of endometriosis is also limited.

Aromatase inhibitors (AI)
Preparations with the active ingredients anastrozol, letrozol, exemestan suppress the expression of aromatase enzyme which participates in androstendione converting to estrone. As application of AI does not lead to ovarian suppression, but, by feedback, to stimulation of ovaries and ovulation, this treatment is only suitable for postmenopausal women (where occurrence of ETRS is approximately 2%) and for women after surgical castration with relapse of endometriosis.

Analgesic treatment

In therapy of cyclical pelvic pain, analgesic treatment is supplementary to hormonal therapy. Non-steroid anti-inflammatory drugs (NSAIDs) have a medium-strong analgesic effect, and – unlike opioid analgesics – are not addictive and do not affect the breathing center, which is an advantage in the treatment of chronic pain. NSAIDs inhibit cyclooxygenase, the enzyme responsible for synthesis of prostaglandins that are generated at the site of the inflammation. The oldest drug of the NSAID group, acetylsalicylic acid, has a relatively weak analgesic and antiflogistic effect. Indometacin and ibuprofen have a stronger effect and are also much better tolerated. In the 70s diclofenac was introduced, and in the 80s two isoforms of cyclooxygenase – constitutional cyclooxygenase 1 (COX-1), whose presence in the human body is physiological and which is responsible for the synthesis of constitutional prostaglandins, and inducible cyclooxygenase 2 (COX-2), which is over-expressed under some pathological conditions (e.g. inflammation) and leads to synthesis of pro-inflammatory prostaglandins (16). Various NSAIDs inhibit both isoenzymes, in various proportions, from which their effect is derived. One safe analgesic, which

Fig. 1 *Mechanism of the effect of NSAIDs*



effectively blocks COX-2 and the synthesis of pro-inflammatory prostaglandins while not inhibiting COX-1 at all, is the selective inhibitor of COX-2 (meloxicam, nimesulid), which is characterized by a significantly lower risk of developing severe gastrointestinal adverse effects (17,18).
Treatment with NSAIDs may provoke various dyspeptic problems and lesions of the stomach lining, together referred to as NSAID gastropathy. In recent years, with application of slow release forms of NSAIDs that only dissolve in small intestine, NSAID enteropathy has also been described. Defects of renal function up to nefropathy may also occur, as well as hemorrhaging conditions, provocation of bronchoconstriction, allergic reactions, hepatopathy or hematopoietic defects. Moreover, some specific adverse effects have been discussed in connection with introducing COX-ibs into clinical practice. Most attention is devoted to the increased risk of cardio-vascular events, which is subject to clinical studies that are currently taking place.

Other modalities of treatment of endometriosis

Immunomodulating therapy (rheologic agents, vasodilatants) affects the production of inflammatory mediators, the size of ETRS deposits and their vascularisation; alternative therapy involves reflexology, acupuncture, homeopathy, traditional Chinese medicine procedures or herbal cures. Because of the chronic and relapsing character of the disease, it seems beneficial to expand the therapeutic possibilities for ETRS to include these nutritional and supplementary therapies, relieving the pain syndromes.

Conclusion

According to the latest theories, endometriosis is a diverse and systemic disease, originating on the basis of a pathological condition of the immunity system, where a genetic element also participates.
Presently there is no possibility of permanently curing endometriosis. According to recent information from the American Society for Reproductive Medicine, endometriosis "should be viewed as a chronic disease requiring a long-term treatment plan aimed a making maximum use of pharmaceutical treatment and limiting repeated surgical procedures" (19). Selected therapy should also be based on specific symptoms and the needs of each patient.

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