Role of medical therapy in the management of uterine adenomyosis

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Adenomyosis is a benign uterine condition affecting women at various ages with different symptoms. The management of these patients is still controversial. Few clinical studies focusing on medical or surgical treatment for adenomyosis have been performed. No drug is currently labelled for adenomyosis and there are no specific guidelines to follow for the best management. Anyhow, medical treatments are effective in improving symptoms (pain, abnormal uterine bleeding and infertility). The rationale for using medical treatment is based on the pathogenetic mechanisms of adenomyosis: sex steroid hormones aberrations, impaired apoptosis, and increased inflammation. Several nonhormonal (i.e., nonsteroidal anti-inflammatory drugs) and hormonal treatments (i.e., progestins, oral contraceptives, gonadotropin-releasing hormone analogues) are currently used off-label to control pain symptoms and abnormal uterine bleeding in adenomyosis. Gonadotropin-releasing hormone analogues are indicated before fertility treatments to improve the chances of pregnancy in infertile women with adenomyosis. An antiproliferative and anti-inflammatory effect of progestins, such as dienogest, danazol and norethindrone acetate, suggests their use in medical management of adenomyosis mainly to control pain symptoms. On the other hand, the intrauterine device releasing levonorgestrel resulted is extremely effective in resolving abnormal uterine bleeding and reducing uterine volume in a long-term management plan. Based on new findings on pathogenetic mechanisms, new drugs are under development for the treatment of adenomyosis, such as selective progesterone receptor modulators, aromatase inhibitors, valproic acid, and anti-platelets therapy (Fertil Steril® 2018;109:398–405. ©2018 by American Society for Reproductive Medicine.)
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Adenomyosis is a uterine disorder characterized by pelvic pain symptoms, abnormal uterine bleeding (AUB), and infertility (1). The clinical presentation is often mixed, and thanks to the improvement in imaging diagnostic accuracy (2–4), adenomyosis may be detected also in a relatively high proportion of asymptomatic women (5). Depending on a woman's age, reproductive status, and clinical symptoms, adenomyosis may also require a life-long management plan, where medical, surgical, and infertility treatment may play a role, alone or in combination (6).

The disease is no longer considered typical of women over 40 years of age and around 30% of young women are affected by adenomyosis (7–9). Moreover, adenomyosis is diagnosed in 22% of infertile women less than 40 years old undergoing assisted reproductive technologies (ART) (10). Thus, a conservative management aiming to preserve or restore fertility and manage clinical symptoms should be considered. In addition, adenomyosis very often coexists with other gynecological comorbidities, such as endometriosis and uterine fibroids, conditions to be considered in the management plan (11, 12).

Although few randomized double-blind clinical studies focusing on medical treatment for adenomyosis have been performed, nowadays medical therapy shows increasing efficacy in patients requiring control of symptoms or fertility treatments. However, no drug is currently labelled for adenomyosis and there are no specific guidelines to follow for the best management. The intended outcome of treating symptomatic adenomyosis is the relief of signs and symptoms, maintenance or improvement of fertility, while minimizing side effects.

The rationale for using medical treatment is based on the pathogenetic mechanisms of adenomyosis, most of them shared with endometriosis.

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Adenomyosis in fact is a sex steroid hormone-dependent disorder, characterized by increased inflammation, impaired apoptosis, and neuroangiogenesis (13). Several nonhormonal (i.e., nonsteroidal anti-inflammatory drugs [NSAIDs]) and hormonal treatments (i.e., progestins, oral contraceptives, gonadotropin-releasing hormone [GnRH] analogues) (14) are currently used off-label to control pain symptoms and AUB in adenomyosis (15). New insight in adenomyosis pathogenesis and new potential therapeutic targets have been identified through animal and in vitro studies, thus it is hoped that they will lead to further clinical studies on new compounds and treatment targets in this heterogeneous disease.

GnRH ANALOGUES

The rationale for using GnRH analogues for medical treatment of adenomyosis is the direct antiproliferative effect within the myometrium through the action on the GnRH receptors expressed by adenomyotic lesions, together with a systemic and local hypoestrogenic effect through a central downregulation and a deep suppression of gonadotropin secretion (16, 17). In fact, adenomyosis is characterized by an hyperestrogenism due to an increased expression of estrogen receptors, an activation of sulphatase and aromatase and a reduced local catabolism of estrogens. This condition, in turn, contributes to induce a down-regulation of progesterone receptors, a loss of their action, and finally, progesterone resistance (13). However, GnRH analogues also act on other pathogenetic mechanisms, by inducing apoptosis in adenomyotic tissues, reducing inflammation and angiogenesis (18). In addition, GnRH analogues are able to markedly reduce the expression of nitric oxide synthases and peroxynitrite, suppressing the serum levels of nitrite/nitrate, stable metabolites of nitric oxide, which are usually increased in adenomyosis (19).

The first reported case of adenomyosis treated using GnRH analogues showed a significant reduction of uterine volume, with relief of severe symptoms (20). Goserelin, leuprolide and nafarelin are commonly used in clinical practice (14), causing uterine size reduction and an improvement in pelvic pain and bleeding (20–22) (Table 1). However, the use of GnRH analogues is associated with hypoestrogenic side effects, including vasomotor syndrome, reduced bone mineral density, genital atrophy, and mood instability. Therefore, an add-back therapy should be used to minimize side effects, even if a long-term treatment with GnRH analogues should be restricted to women unresponsive to other medications or in surgically high-risk patients. However, there is no specific indication on when and which type of add-back therapy should be used in case of severe vasomotor symptoms or to prevent bone loss when GnRH analogues are prescribed for adenomyosis (23). The option to use long-term, low-dose GnRH analogues, so-called draw-back therapy, was tested in a small sample of women with adenomyosis. Buserelin acetate per nasal administration for 2 years allowed maintenance of plasma estradiol levels within the therapeutic window, suppressing adverse events while maintaining therapeutic effects on adenomyosis (24).

PROGESTINS

Norethindrone Acetate

The rationale for using norethindrone acetate (NETA) is based on the observation that progestins are able to inhibit estradiol-induced vascular endothelial growth factor and stromal cell-derived factor 1 in human endometrial stromal

TABLE 1

Summary of commonly used drugs for adenomyosis.

Class of compound	Mechanisms of action	Effects	Side effects
GnRH analogues	Hypoestrogenic state Antiproliferative effect Increased apoptosis	Significant reduction of uterine size, bleeding and pain in short term period Improvement of pregnancy rate in ART cycles	Menopausal symptoms (i.e., vasomotor syndrome, reduced bone mineral density, genital atrophy, mood instability) Consider add-back therapy for prolonged treatment
Progestins	Decidualization and then atrophy of endometrial tissue Mild hypoestrogenism Antiproliferative effect Anti-inflammatory effect	Significant reduction of pain and bleeding	Breakthrough bleeding
LNG-IUS	Endometrial atrophy Direct local action on adenomyotic foci	Significant reduction of menstrual loss, with increase in hemoglobin, hematocrit and ferritin Decreased uterine volume and pain symptoms	Irregular bleeding Amenorrhea
COCs	Decidualization and subsequent atrophy of the endometrium	Benefit from the resulting amenorrhea	Spotting Headache Thromboembolic events
NSAIDs	Reduced prostaglandins synthesis	Reduced pain and bleeding	Gastrointestinal side-effects

Note: COCs = combined oral contraceptives; GnRH analogues = gonadotropin releasing hormone analogues; LNG-IUS = levonorgestrel-releasing intrauterine system; NSAIDs = nonsteroidal anti-inflammatory drugs.

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