Titolo rivista/libro: Journal of endometriosis Online

Titolo articolo/sezione: Current and future medical treatment of adenomyosis

Autore/i: C. C. Tosti

ISSN: 2036-282X

DOI:

Anno: 2016

Volume: 8

Fascicolo: 4

Editore:

Pag. iniziale: 127

Pag. finale: 135

JEPPD
ISSN 2284-0265

Journal of Endometriosis and Pelvic Pain Disorders 2016; 8(4): 127-135
DOI: 10.5301/je.5000261

REVIEW

Current and future medical treatment of adenomyosis

Claudia Tosti, Libera Troìa, Silvia Vannuccini, Lucia Lazzeri, Stefano Luisi, Felice Petraglia

Department of Molecular and Developmental Medicine, Obstetrics and Gynecology, University of Siena, Siena - Italy

ABSTRACT

Adenomyosis is a benign gynecological disorder associated with abnormal uterine bleeding, dysmenorrhea, dyspareunia and infertility, requiring a life-long management plan through medical or surgical treatment. The choice depends on woman's age, reproductive status and clinical symptoms. However, until now no drug labelled for adenomyosis is available; thus, the present review will focus on medical treatments currently used for adenomyosis and those in development.

Adenomyosis may be considered a sex steroid hormone-related disorder associated with an intense inflammatory process. The use of gonadotropin-releasing hormone agonists (GnRH-a) for treating adenomyosis is described blocking the hypothalamic-pituitary-gonadal axis; however, it has long been associated with frequent and intolerable hypoestrogenic side effects. An antiproliferative effect of progestins suggests their use for treating adenomyosis, reducing bleeding and pain. Continuous oral norethisterone acetate or medroxyprogesterone acetate may help to inducing regression of adenomyosis, relief pain and reduce bleeding. The use of vaginal danazol has therapeutic effect on adenomyosis combining progestogenic and anti-inflammatory activity. The intrauterine device releasing levonorgestrel (Lng-IUD) is widely assessed in menorrhagia, and has been shown to be extremely effective in resolving pain and bleeding symptoms associated with adenomyosis. Recent data show a therapeutic effect of dienogest on adenomyosis symptoms.

New drugs are under development for the treatment of adenomyosis, such as aromatase inhibitors (AIs) and selective estrogen receptor modulators (SERMs), that produce a hypoestrogenic environment reducing pain, but are correlated with some adverse effects and a recurrence of symptoms after discontinuation of treatment. Selective progesterone receptor modulators (SPRMs) may reduce adenomyosis-associated pelvic pain, by inhibiting endometrial proliferation and suppressing adenomyotic lesion growth, as shown in animal models; however, the long-term effect with SPRMs needs further determination.

Keywords: Adenomyosis, Danazol, Dienogest, GnRH agonists, Medical treatment, Progestin

Introduction

Adenomyosis is a common benign gynecological disorder, characterized by the presence of endometrial glands and stroma within the myometrium. The reported incidence varies widely, between 5% and 70% (1-4), suggesting that the actual occurrence of adenomyosis is not well known. Classically, the definitive diagnosis is based on histological examination after hysterectomy and the prevalence of adenomyosis being calculated in women who undergo hysterectomy represents a consistent confounding bias. On this basis, the incidence of adenomyosis in the general population seems to be misrepresented as affecting mainly 35- to 50-years-old multiparous women with menorrhagia and dysmenorrhea and short menstrual cycles (≤24 days in length) (5, 6).

Accepted: November 17, 2016
Published online: December 20, 2016

Corresponding author:
Felice Petraglia
Department of Molecular and Developmental Medicine
Obstetrics and Gynecology, University of Siena
Policlinico "Santa Maria alle Scotte"
Viale Bracci
53100 Siena, Italy
felice.petraglia@unisi.it

Pathogenesis of adenomyosis

A current hypothesis suggests that adenomyosis is associated with endometrial invasion of the myometrium following physiological or surgical uterine procedures, since endometrium may invade a predisposed or traumatized endometrial-myometrial interface (7). Another major pathogenetic mechanism suggests adenomyosis as a sex hormone-related disorder, in fact and the most common used drugs are targeted for modulating estrogen/progesterone receptors (ER/PR). Polymorphisms in the ER-α gene are associated with a risk of adenomyosis (8). Adenomyotic tissue contains steroid receptors, also showing an increased activity of aromatase and sulfatase enzymes (8). Together with the circulating estrogen, locally produced estrogens stimulate the growth of adenomyotic tissue mediated by the ER (9). The regulation of

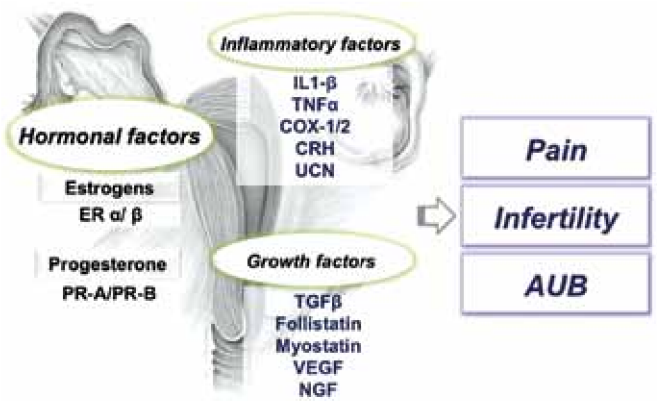

Fig. 1 - Pathogenesis of adenomyosis. AUB = abnormal uterine bleeding; TNFα = tumor necrosis factor alpha; VEGF = vascular endothelial growth factor; NGF = nerve growth factor; CRH = corticotropin-releasing hormone; UCN = urocortin; COX = cyclooxygenase; ER = estrogen receptor; PR = progesterone receptors.

17beta-hydroxysteroid dehydrogenase type 2 (17beta-HSD2) is also altered in the eutopic endometrium of women with adenomyosis suggesting a decreased local estrogen metabolism (10). Hyperestrogenism is due to the action of aromatase and sulfatase enzyme converting estron-3-sulfate in estrone, explaining the increased levels of E2 in menstrual blood, but not in peripheral blood of women with adenomyosis. The reduced expression of PR can be related to the development and progression of adenomyosis and may explain the action of progestin agents on adenomyosis (11) (Fig. 1).

Endometrial microenvironment in adenomyosis differs in some aspects of cellular and humoral immunity from the endometrium of unaffected women and is associated with aberrant immune responses (12). In adenomyosis, metabolic and molecular abnormalities are often similar to those observed in endometriosis, including increased angiogenesis and proliferation (13). An increased expression of growth factors (transforming growth factor β family) has been shown to play a role in the development of adenomyosis. Myostatin, follistatin and activin A are hyper-expressed by adenomyotic nodule and may affect proliferation of endometrial glands/stroma and of surrounding myometrial cells (14). Similarly, vascular endothelial growth factor (VEGF) is one the most important factors inducing angiogenesis and promoting the growth of ectopic endometrial glandular epithelial cells. VEGF promotes the ability of cell proliferation and vessel infiltration into the myometrium, thereby increasing the depth and scope of the lesion and consequently the bleeding (15, 16) (Fig. 1). In addition, a deregulation of cell pathways, such as mitogen-activated protein kinases/extracellular signal-regulated kinases (MAPKs/ERKs), was observed in uterine smooth muscle cell cultures from myometrium of women with adenomyosis (17).

An aberrant behavior of endometrial stromal cells (ESCs) may play a role in the formation of ectopic endometrial implants in adenomyosis. IL-6 mRNA was significantly expressed in endometrial stromal cell ESCs after in vitro culture with macrophage in adenomyosis (18). An abnormal expression of nerve growth factor (NGF) is also described in adenomyosis, promoting cell proliferation and aromatase synthesis and an increase in cytokines and inflammatory mediators and alterations of adhesion molecules have also been observed (19) (Fig. 1).

Symptoms and diagnosis of adenomyosis

Adenomyosis is associated with pain, infertility and abnormal uterine bleeding (AUB) (20, 21). The high expression of NGF, synaptophysin (SYN), and microtubule-associated protein 2 (MAP2) mRNA in adenomyotic nodules supports a possible neurogenesis in adenomyosis, thus contributing to explain the associated pain (dysmenorrhea, dyspareunia). The high expression of corticotropin-releasing hormone (CRH) and urocortin (Ucn) in adenomyosis may also be correlated with increased prostaglandin synthesis, since in other tissues, a stimulatory effect of CRH/Ucn on cyclooxygenase 2 (COX-2) has been shown. The neuropeptides/neurogenetic activation is a major event in deep infiltrating endometriosis correlated with hyperalgesia and may explain the adenomyosis-induced pain symptoms (19) (Fig. 1).

Adenomyosis is associated with a reduction of 28% (95% CI, 5%-45%) in the likelihood of clinical pregnancy in infertile women who underwent in vitro fertilization/intracytoplasmic sperm injection (IVF/ICSI) with autologous oocytes (22). Indeed, a more than doubled risk of miscarriage was observed, suggesting that the adenomyotic uterine environment increases the risk of miscarriage independently of oocyte and embryo quality. In general, the detrimental effect of adenomyosis on IVF/ICSI outcome is related to both reduced probability of clinical pregnancy and increased risk of early pregnancy loss. There are various possible biological interpretations for this effect, including the chronic inflammatory condition caused by infiltration of endometrial glands in the myometrium (23), the increased local estrogen production due to aromatase P450 (CYP19A1) overexpression (24), dysperistalsis resulting in impaired utero-tubal rapid sperm transport (25), and alterations of adhesion molecules, cell proliferation, apoptosis, and free radical metabolism (12). A significant reduction of live birth rate per cycle in women with adenomyosis compared with those without the condition is reported (26).

AUB is a typical presentation of adenomyosis, with menorrhagia and metrorrhagia, representing one of the most common causes of AUB by PALM-COEIN FIGO classification (27). A significant positive correlation between the severity of adenomyosis on ultrasound and the amount of menstrual loss estimated using pictorial blood loss assessment charts was observed (28).

During the last decade, the progress of imaging techniques has allowed non-invasive diagnosis of adenomyosis. Magnetic resonance imaging (MRI) provides an accurate diagnosis in symptomatic women, with 80% overall accuracy (29, 30). In particular, MRI may allow visualization of a specific uterine compartment at the endomyometrial junction zone (JZ), whose focal or diffuse thickening with low signal intensity on T2-weighted images is related to adenomyosis (31, 32). In parallel, specific criteria were proposed for the diagnosis of adenomyosis using two-dimensional (2D) transvaginal ultrasound (TVS), with sensitivity and specificity comparable to those of

MRI (33, 34) and the three-dimensional (3D) allowing clearer visualization of the JZ (35, 36). Following these technical developments, the detection of adenomyotic features at imaging is becoming common and the association with menstrual pain (37, 38), heavy menstrual bleeding (28) and infertility (21) may facilitate the diagnosis of adenomyosis. There was a 34% incidence of adenomyosis in nulligravid women aged 18-30 years (39). Therefore, sonographic features suggestive of diffuse adenomyosis may help to perform early diagnosis in fertile women, in particular in symptomatic nulliparous women.

Concerning serum biomarkers of adenomyosis, evidence is still poor with the exception of Ca-125 (40). A recent study reported that serum levels of osteopontin, a multifunctional cytokine implicated in acute and chronic inflammation as well as in cell migration and metastatic dissemination, are significantly decreased in women with focal forms of adenomyosis compared to women with no adenomyosis (41). However, serum biomarkers still belong to the research field and are currently not used in clinical practice for diagnosis of adenomyosis.

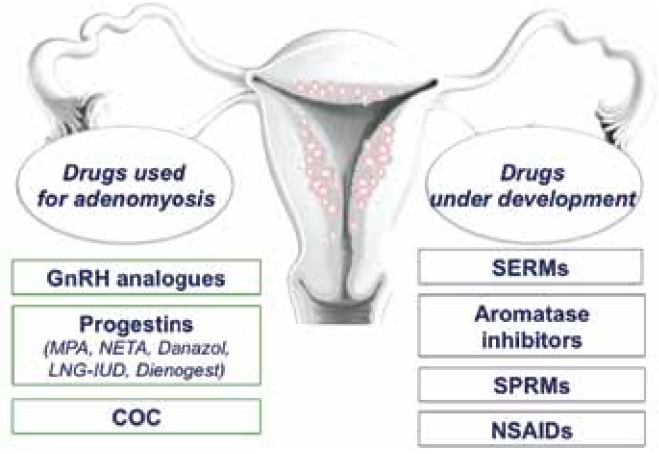

Fig. 2 - Drugs used or under development for treating of adenomyosis-related symptoms. SERMs = selective estrogen receptor modulators; COC = oral contraceptive; NSAIDs = nonsteroidal anti-inflammatory drugs; SPRMs = selective progesterone receptor modulators; GnRH = gonadotropin-releasing hormone.

Current medical treatments

Adenomyosis may require long-term strategies and an integrated approach, including medical treatments alone or with a combined infertility technique, and surgical treatment (42-44). The management of patients with adenomyosis is difficult and conservative treatment is required for those who require preservation of fertility and improvement of quality of life. Minimally invasive surgical procedures enable conservative options, including endometrial ablation and resection, laparoscopic excision of adenomyosis and MRI-guided focused ultrasound (45-47).

No drug currently available is labelled for the treatment of adenomyosis and no specific guidelines refer on the management of the disease.

The objectives of medical treatment are to reduce pain and AUB and restore fertility. The present medical treatments for adenomyosis follow the principles of the management of endometriosis, which are usually aimed at reducing the production of endogenous estrogen or inducing endometrial differentiation with progestins (48). For this reason, the hormonal medications commonly used in the treatment of adenomyosis are similar to those for endometriosis and include gonadotropin-releasing hormone agonists (GnRH-a), progestins (danazol, levonorgestrel-IUD, dienogest), and oral contraceptives (COC) (49, 50).

However, in fertile patients with desire of pregnancy all the available hormonal treatments, despite the reduction of pain and bleeding, have the side effect to be contraceptive.

Non-hormonal medications, such as pro-coagulating agents, iron supplementation and nonsteroidal anti-inflammatory drugs (NSAIDs), are also aimed at controlling symptoms of AUB and pain in adenomyosis (51, 52) (Fig. 2).

There are few well designed randomized controlled trials on medical or surgical management of adenomyosis with long-term outcomes, including fertility and pregnancy. Since 2006 there has existed a paucity of clinical studies to guide treatment and the information collected from published studies is insufficient. Several therapeutic targets have been identified through animal and in vitro studies, and it is hoped that they will lead to further clinical studies on new compounds and treatment targets in this heterogeneous disease (43, 49).

GnRH agonist (GnRH-a)

Mechanism of action

GnRH-a are drugs used for the treatment of adenomyosis because, binding to the GnRH receptors in the pituitary gland, they cause a downregulation of GnRH activity, and induce a reversible state of medical menopause. Estrogen levels fall, inducing atrophy of the adenomyotic lesions, which in turn results in a reduction in the uterine size. GnRH agonist in fact decreases expression of aromatase cytochrome P450 in eutopic endometrium, mainly by promoting a hypoestrogenic state (53). GnRH-a inhibits cell proliferation and increases the apoptotic rate in eutopic endometrial cell cultures, an effect that appears to be mediated by an increase in the expression of the pro-apoptotic proteins Bax and FasL and a decrease in the expression of the anti-apoptotic protein Bcl-2, also affecting inflammatory pathways (54, 55). Indeed, in adenomyotic lesions and eutopic endometrium and myometrium, the treatment with GnRH-a was demonstrated to be able to significantly suppress tissue expression of heat shock protein 70 (HSP70), decreasing the tissue stress reaction observed in adenomyosis (56).

Clinical studies

The first reported case of adenomyosis treated using GnRH-a was published in 1991 and the results showed a reduction in uterine volume from 440 to 150 cm^3, with relief of severe symptoms. However, on discontinuation of therapy, the symptoms recurred and uterine volume increased

(57). Some observational studies have shown that GnRH-a is effective against adenomyosis-related pain, and consequently contributes to the achievement of successful pregnancies and live births (58-61). Goserelin, leuprolide and nafarelin are commonly used in clinical practice (62). In assisted reproductive technologies (ART), long agonist stimulation protocols and pretreatment with GnRH-a for differed embryo transfer improve pregnancy rates (61). However, the use of GnRH-a is associated with hypoestrogenic side effects, including vasomotor syndrome, reduced bone mineral density, genital atrophy, and mood instability. To minimize the GnRH-a-inducing adverse events, an add-back therapy with various kinds of hormone preparations has been successfully used recently and enables an indefinite extension of the GnRH-a treatment period that, however, should be used only in highly selected women unresponsive to other medications or in surgically high-risk patients (43).

Progestins

Mechanism of action

Progestins action involves the decidualization and subsequent atrophy of endometrial tissue, modulation of mitotic activity, local growth factors and their receptors, as well as other paracrine mechanisms and anti-inflammatory mechanisms (63, 64).

Clinical studies

The use of progestins for adenomyosis-associated pain and AUB is common, but no randomized clinical trials have been done. Concerning side effects, progestins are known to cause breakthrough bleeding and other less frequent symptoms, such as changes in menstrual flow, amenorrhea, changes in cervical secretions, edema, weight gain or loss, cholestatic jaundice, allergic rash with or without pruritus, melasma or chloasma and mental depression (63, 64).

Progestins used for adenomyosis

Norethindrone acetate (NETA)

Mechanism of action

NETA inhibits estradiol-induced vascular endothelial growth factor and stromal cell-derived factor 1 in human endometrial stromal cells (65).

Clinical studies

Use of NETA in adenomyosis is associated with a marked degree of pain relief and satisfaction, although the efficacy seems to be more gradual, but progressively better with a longer duration of use (62). The role of NETA in the management of adenomyosis has been demonstrated in women presenting moderate or severe pelvic pain and bleeding, with a significant improvement of both dysmenorrhea and bleeding after treatment (dose 5 mg/day) (66). The progestin treatment started at the beginning of the menstrual cycle, and was taken orally as a three-weeks-on and one-week-off regime. Since maximum response was obtained at 3 months, NETA may be considered an effective, well-tolerated and inexpensive medical treatment for adenomyosis, with fewer and milder side effects (66). A drawback of NETA therapy is the reduction of libido in about one-fifth of women (9).

Danazol

Mechanism of action

Danazol has a complex mechanism of action on steroidogenesis, lowering the mid-cycle luteinizing hormone surge, and increasing serum free testosterone levels (62). Danazol acts directly on adenomyotic tissue in vitro to inhibit DNA synthesis and induce apoptosis, and its use results in an androgenic and hypoestrogenic environment; the former might have a more direct effect on adenomyotic lesions and reduce pain during and after therapy, and the latter may have an indirect effect on adenomyotic lesions (43). Danazol has anti-inflammatory effects in vitro, and in vivo effects decreasing the production of prostaglandins and cytokines; indeed, danazol significantly inhibits lymphocyte proliferation, reduces monocyte-enhanced endometrial proliferation in peripheral blood and increases peritoneal macrophage cytotoxicity (67-69).

Clinical studies

The use of danazol is associated with relieved pain and clinical improvement in 55%-93% of adenomyosis patients treated for 6 months (43). However, danazol is not suitable for prolonged use partly because of its adverse side effects. A low-dose danazol (200 mg/day) was daily administered by vaginal route for 6 months in young women with adenomyosis and the severity of blood loss and uterine volume were significantly reduced (70). Hematocrit, hemoglobin, and red blood cell count increased in all treated women after 6 months; the treatment did not affect hormonal parameters, and menstrual cycle remained unaffected. Few local vaginal adverse effects were recorded (70).

Levonorgestrel-releasing intrauterine system (LNG-IUS)

Mechanism of action

Multiple mechanisms may explain the role of the LNG-IUS in adenomyosis (71). After insertion of the system a decidualization of the endometrium, followed by atrophic changes, is observed, producing a marked reduction in menstrual blood loss (72). Through absorption within the myometrium, the progestin also acts directly on the adenomyotic foci. In addition, downregulation of ER, in both glandular and stromal endometrial layers, occurs shortly after placement of the device and persists for at least the first year of use (73). Treatment with the LNG-IUS also resulted in reduced lymphangiogenesis and lymphovascular density in the endometrial and myometrial tissues of patients with adenomyosis (74).

Clinical studies

Evidence supports that LNG-IUS is used as an effective treatment reducing adenomyosis-associated menorrhagia with a significant increase in hemoglobin, hematocrit and serum ferritin (71, 75). The efficacy of the LNG-IUS treatment has been widely assessed in decreased abnormal uterine bleeding and uterine volume at 12 months, and has been extremely effective in resolving pain associated with adenomyosis (moderate or severe dysmenorrhea and dyspareunia) (76). LNG-IUS reduces abnormal uterine bleeding secondary to endometrial dysfunction more effectively than oral contraceptives, luteal-phase oral progestins, or NSAIDs (76, 77). There was no significant difference between LNG-IUS and GnRH-a (leuprorelin) in reducing endometriosis- and/or adenomyosis-related pain during the 6 months' treatment (78). Adenomyotic lesions are reduced in size, uterine contractility improves and the uterine size decreases (49). The positive effect of LNG-IUS on dysmenorrhea is probably mediated through a reduction of prostaglandin production within the endometrium; reduction in the size and activity of adenomyotic tissue may also account for the improvement in dysmenorrhea (79, 80). Irregular bleeding and amenorrhea are the main side effects during the first few months.

Dienogest

Mechanism of action

Dienogest has been reported to exhibit high selectivity for binding to progesterone receptors (81, 82) and inhibitory effects on the secretion of cytokines in endometriotic stromal cells (83). It directly inhibits cellular proliferation and also induces apoptosis in human adenomyotic stromal cells (84). On the other hand, dienogest causes a mild inhibition of ovarian function, with low hypoestrogenic symptoms and minimal effect on bone mineral density, which can be explained by mild suppression of estradiol (85).

Clinical studies

In a pilot study, dienogest was effective in alleviating the pain symptoms associated with adenomyosis and uterine fibroids (86). A prospective clinical trial compared the efficacy of oral dienogest (2 mg/day) in comparison to triptorelin acetate (TA) injection (3.75 mg/4 weeks, subcutaneously) for the treatment of premenopausal menorrhagia and pelvic pain in women with uterine adenomyosis. Significant reductions in pelvic pain after 16 weeks of treatment were obtained in both groups, demonstrating the equivalence of dienogest relative to TA, which was more effective in controlling menorrhagia and reducing uterine volume (85).

Oral contraceptives (COCs)

Mechanism of action

COCs are used in the management of adenomyosis-related pain and AUB to induce a decreased menstruation, causing decidualization and subsequent atrophy of the endometrium. Aromatase expression in the eutopic endometrium and adenomyotic foci is suppressed by COCs (87).

Clinical studies

No well conducted randomized controlled trials are reported on the pharmacological treatment of adenomyosis using COCs. Patients with dysmenorrhea and menorrhagia may benefit from the resulting amenorrhea, which may provide relief of symptoms (88). The off-label use of COCs for adenomyosis-related symptoms enables satisfactory long-term pain control similar to other drugs, but they are less expensive, with the possibility to be used for longer periods of time (89). However, many patients report irregular bleeding and it should be emphasized that COCs have been often associated with an increased risk of venous thrombosis, and are not suggested in patients with other risk factors (thrombophilia or hypertension) (88). An individualized, medical long-term treatment concept to control adenomyosis-related symptoms in women who do not desire to become pregnant needs to be further studied.

Future medical treatments

Several studies are on-going in order to develop new drugs for the treatment of adenomyosis. Selective estrogen receptor modulators (SERMs), selective progesterone receptor modulators (SPRMs) and aromatase inhibitors (AIs) are the main drugs under investigation (Fig. 2).

Selective estrogen receptor modulators (SERMs)

Mechanism of action

For the treatment of adenomyosis, the ideal SERM might have antagonistic activity in the endometrium (adenomyotic lesion) and agonistic activity for bone and lipids. Basic clinical studies indicate major roles for estrogen and progesterone in the pathology of adenomyosis. According to the observation that estrogen-induced epithelial-mesenchymal transition (EMT) in endometrial epithelial cells contributes to the development of adenomyosis based on the following evidence: (i) E-cadherin was downregulated and vimentin was upregulated in the epithelial compartment of adenomyotic lesions; (ii) changes in EMT markers were associated with the serum estradiol (E2) levels; (iii) estrogen induced EMT migration and invasion of ER-positive endometrial cells, and such effects were abrogated by a SERM; and (iv) estrogen-dependent adhesion of xeno-transplant endometrial fragments to the peritoneal cavities of mice was observed, SERMs may be a potential therapeutic agent for adenomyosis patients (90). The mechanisms of the tissue-selectivity can be explained by three interactive mechanisms, including differential ER expression in a given target tissue, differential ER conformation on ligand binding, and differential expression and binding to the ER coregulator proteins, which are considered potentially effective therapy for women with adenomyosis (91-94).

Clinical studies

There are no well conducted randomized controlled trials on the pharmacological treatment of adenomyosis with SERMs.

Aromatase inhibitors (AIs)

Mechanism of action

Aromatase cytochrome P450 (CYP19A1) is a key enzyme in the synthesis of estrogen from androgens, involving the conversion of androstenedione and testosterone to estrone and E2, respectively (95). CYP19A1 is immunohistochemically localized in the cytoplasm of glandular cells of adenomyotic tissues and of eutopic endometrium from patients with this disease (96). It is an excellent target for inhibition of the E2 synthesis because it is the final step in steroid biosynthesis; therefore, there are no important downstream enzymes to be affected (95).

Clinical studies

A single clinical trial employing AIs in the management of adenomyosis has been done (97). A prospective randomized controlled study compared the efficacy of letrozole versus GnRH-a for 12 weeks in treating premenopausal women with uterine adenomyosis, with no significant difference in total uterine size based on post-treatment uterine volumes in the two group; however, total adenomyoma volume decreased in both group. AIs demonstrated the same efficacy as GnRH-a in reducing adenomyoma volume and improving symptoms (97). A case report outlined the effect of anastrozole with GnRH-a for severe symptomatic adenomyosis in a woman of reproductive age who wished to maintain her fertility and that was refractory to GnRH-a and danazol, demonstrating reduction of uterine volume as estimated by MRI, ultrasonography, and symptom improvement (98).

The side effects most commonly associated with AI treatments are headaches, hot flashes, mood changes, muscle aches and breakthrough bleeding. Estradiol levels are significantly suppressed with this treatment, avoiding vasomotor symptoms and agonist flare-up effects (97). Furthermore, their use would be interesting in obese patients due to antiestrogenic action on both ovarian and adipose tissues. AIs thus appear to have a promising future for adenomyosis in cases of resistance to other treatments and additional studies are needed.

Selective progesterone receptor modulators (SPRMs)

Mechanism of action

SPRMs are defined as a new class of progesterone receptor ligands, which exhibit both progesterone agonist and antagonist activities in the endometrium, reducing pain, bleeding, cell proliferation and inhibiting inflammation (99). This property justifies their use in the treatment of myomas or endometriosis (100, 101). Mifepristone influences the caspase 3 expression in adenomyosis tissue. The expression of caspase 3, examined in both eutopic and ectopic endometrium, was significantly increased in three groups that were treated, respectively, with 5, 10 and 15 mg of mifepristone compared to placebo group. Mifepristone can also induce cell apoptosis, inhibiting the onset and development of adenomyosis (102).

Clinical studies

SPRMs require investigations and well designed, randomized controlled trials to assess their long-term effects and their clinical use in patients with adenomyosis.

New anti-inflammatory drugs

Mechanism of action

Increased expression of growth factors has been shown to play a role in the development of adenomyosis (14). Myostatin, follistatin, and activin A are hyper-expressed by adenomyotic nodule and may affect proliferation of endometrial glands/stroma and of surrounding myometrial cells (14). Increased expression of interleukin 10 (IL-10) (103) and tumor necrosis factor-α (TNF-α) (101), as well as altered expression of cyclooxygenase-2 (COX-2) (104), suggest an involvement in inflammatory pathway in adenomyosis. Abnormal expression of NGF is also described in adenomyosis, as well as in animal model of adenomyosis (105); endometrial stromal cells express NGF, promoting cell proliferation and aromatase synthesis (106). The increased IL-1b in adenomyosis supports the evidence of increased TNF-α activity in these lesions affecting nuclear factor-kB (NF-kB), binding activity correlated positively with the severity of dysmenorrhea in adenomyosis (107). The high expression of NGF, SYN and MAP-2 mRNA in adenomyotic nodules supports a possible neurogenesis in adenomyosis, thus contributing to explain the associated pain (19).

Clinical studies

Several studies have demonstrated that NSAIDs are effective in reducing menstrual blood loss. NSAIDs reduce prostaglandin synthesis at the level of the endometrium by inhibiting cyclooxygenase. Endometrial prostaglandin receptors may play a role in developing aberrant vascularization and promoting neoangiogenesis, which can result in AUB (108). Thus, the inhibition of prostaglandin synthesis aids in reducing menstrual bleeding. NSAIDs seem to be superior to placebo or comparable to other medical treatments (52). NSAIDs are considered an appropriate medication for heavy menstrual bleeding, while also alleviating dysmenorrhea.

Conclusions

The medical treatment of adenomyosis is an open field with a great possibility of new advancement. No double-blind placebo-controlled study was ever conducted on the management of adenomyosis and only observational studies are reported in literature. The identification of the pathogenetic mechanisms is allowing using some of current drugs (GnRH-a,

progestins, COC) also for adenomyosis, even if they are labelled for endometriosis or uterine myomas. New molecules are needed and they are under investigation for patients with adenomyosis.

Disclosures

Financial support: No grants or funding have been received for this study.
Conflict of interest: None of the authors has financial interest related to this study to disclose.

References

1. Parazzini F, Mais V, Cipriani S, Busacca M, Venturini P; GISE. Determinants of adenomyosis in women who underwent hysterectomy for benign gynecological conditions: results from a prospective multicentric study in Italy. Eur J Obstet Gynecol Reprod Biol. 2009;143(2):103-106.
2. Vercellini P, Parazzini F, Oldani S, Panazza S, Bramante T, Crosignani PG. Adenomyosis at hysterectomy: a study on frequency distribution and patient characteristics. Hum Reprod. 1995;10(5):1160-1162.
3. Bergholt T, Eriksen L, Berendt N, Jacobsen M, Hertz JB. Prevalence and risk factors of adenomyosis at hysterectomy. Hum Reprod. 2001;16(11):2418-2421.
4. Bird CC, McElin TW, Manalo-Estrella P. The elusive adenomyosis of the uterusrevisited. Am J Obstet Gynecol. 1972;112(5): 583-593.
5. Vercellini P, Viganò P, Somigliana E, Daguati R, Abbiati A, Fedele L. Adenomyosis: epidemiological factors. Best Pract Res Clin Obstet Gynaecol. 2006;20(4):465-477.
6. Templeman C, Marshall SF, Ursin G, et al. Adenomyosis and endometriosis in the California Teachers Study. Fertil Steril. 2008;90(2):415-424.
7. Curtis KM, Hillis SD, Marchbanks PA, Peterson HB. Disruption of the endometrial-myometrial border during pregnancy as a risk factor for adenomyosis. Am J Obstet Gynecol. 2002;187(3): 543-544.
8. Oehler MK, Greschik H, Fischer DC, Tong X, Schuele R, Kieback DG. Functional characterization of somatic point mutations of the human estrogen receptor alpha (hERalpha) in adenomyosis uteri. Mol Hum Reprod. 2004;10(12):853-860.
9. Kitawaki J. Adenomyosis: the pathophysiology of an oestrogen-dependent disease. Best Pract Res Clin Obstet Gynaecol. 2006;20(4):493-502.
10. Kitawaki J, Koshiba H, Ishihara H, Kusuki I, Tsukamoto K, Honjo H. Progesterone induction of 17beta-hydroxysteroid dehydrogenase type 2 during the secretory phase occurs in the endometrium of estrogen-dependent benign diseases but not in normal endometrium. J Clin Endocrinol Metab. 2000; 85(9):3292-3296.
11. Jichan Nie, Xishi Liu, Guo SW. Promoter hypermethylation of progesterone receptor isoform B (PR-B) in adenomyosis and its rectification by a histone deacetylase inhibitor and a demethylation agent. Reprod Sci. 2010;17(11):995-1005.
12. Benagiano G, Brosens I, Habiba M. Structural and molecular features of the endomyometrium in endometriosis and adenomyosis. Hum Reprod Update. 2014;20(3):386-402.
13. Brosens I, Brosens JJ, Benagiano G. The eutopic endometrium in endometriosis: are the changes of clinical significance? Reprod Biomed Online. 2012;24(5):496-502.
14. Carrarelli P, Yen CF, Arcuri F, et al. Myostatin, follistatin and activin type II receptors are highly expressed in adenomyosis. Fertil Steril. 2015;104(3):744-52.e1.
15. Mu Y, Hu X, He J, et al. Serum levels of vascular endothelial growth factor and cancer antigen 125 are related to the prognosis of adenomyosis patients after interventional therapy. Int J Clin Exp Med. 2015;8(6):9549-9554.
16. Huang TS, Chen YJ, Chou TY, et al. Oestrogen-induced angiogenesis promotes adenomyosis by activating the Slug-VEGF axis in endometrial epithelial cells. J Cell Mol Med. 2014;18(7): 1358-1371.
17. Streuli I, Santulli P, Chouzenoux S, Chapron C, Batteux F. Activation of the MAPK/ERK Cell-Signaling Pathway in Uterine Smooth Muscle Cells of Women With Adenomyosis. Reprod Sci. 2015;22(12):1549-1560.
18. Yang JH, Wu MY, Chang DY, Chang CH, Yang YS, Ho HN. Increased interleukin-6 messenger RNA expression in macrophage-cocultured endometrial stromal cells in adenomyosis. Am J Reprod Immunol. 2006;55(3):181-187.
19. Carrarelli P, Chih-Feng Y, Funghi L, et al. Expression of Inflammatory and Neurogenic Mediators in Adenomyosis: A Pathogenetic Role. Reprod Sci. 2016 Jul 20. pii: 1933719116657192. [Epub ahead of print].
20. Struble J, Reid S, Bedaiwy MA. Adenomyosis: A Clinical Review of a Challenging Gynecologic Condition. J Minim Invasive Gynecol. 2016;23(2):164-185.
21. Campo S, Campo V, Benagiano G. Infertility and adenomyosis. Obstet Gynecol Int. 2012;2012:786132.
22. Vercellini P, Consonni D, Dridi D, Bracco B, Frattaruolo MP, Somigliana E. Uterine adenomyosis and in vitro fertilization outcome: a systematic review and meta-analysis. Hum Reprod. 2014;29(5):964-977.
23. Tremellen K, Russell P. Adenomyosis is a potential cause of recurrent implantation failure during IVF treatment. Aust N Z J Obstet Gynaecol. 2011;51(3):280-283.
24. Brosens J, Verhoeven H, Campo R, et al. High endometrial aromatase P450 mRNA expression is associated with poor IVF outcome. Hum Reprod. 2004;19(2):352-356.
25. Kissler S, Hamscho N, Zangos S, et al. Uterotubal transport disorder in adenomyosis and endometriosisa cause for infertility. BJOG. 2006;113(8):902-908.
26. Martínez-Conejero JA, Morgan M, Montesinos M, et al. Adenomyosis does not affect implantation, but is associated with miscarriage in patients undergoing oocyte donation. Fertil Steril. 2011;96(4):943-950.
27. Munro MG, Critchley HO, Broder MS, Fraser IS; FIGO Working Group on Menstrual Disorders. FIGO classification system (PALM-COEIN) for causes of abnormal uterine bleeding in nongravid women of reproductive age. Int J Gynaecol Obstet. 2011; 113(1):3-13.
28. Naftalin J, Hoo W, Pateman K, Mavrelos D, Foo X, Jurkovic D. Is adenomyosis associated with menorrhagia? Hum Reprod. 2014;29(3):473-479.
29. Dueholm M, Lundorf E, Hansen ES, Sørensen JS, Ledertoug S, Olesen F. Magnetic resonance imaging and transvaginal ultrasonography for the diagnosis of adenomyosis. Fertil Steril. 2001;76(3):588-594.
30. Moghadam R, Lathi RB, Shahmohamady B, et al. Predictive value of magnetic resonance imaging in differentiating between leiomyoma and adenomyosis. JSLS. 2006;10(2):216-219.
31. Chopra S, Lev-Toaff AS, Ors F, Bergin D. Adenomyosis: common and uncommon manifestations on sonography and magnetic resonance imaging. J Ultrasound Med. 2006;25(5):617-627, quiz 629.
32. Dueholm M, Lundorf E. Transvaginal ultrasound or MRI for diagnosis of adenomyosis. Curr Opin Obstet Gynecol. 2007;19(6): 505-512.
33. Bazot M, Cortez A, Darai E, et al. Ultrasonography compared with magnetic resonance imaging for the diagnosis of adenomyosis:

correlation with histopathology. Hum Reprod. 2001;16(11): 2427-2433.
34. Kepkep K, Tuncay YA, Göynümer G, Tutal E. Transvaginal sonography in the diagnosis of adenomyosis: which findings are most accurate? Ultrasound Obstet Gynecol. 2007;30(3):341-345.
35. Exacoustos C, Brienza L, Di Giovanni A, et al. Adenomyosis: three-dimensional sonographic findings of the junctional zone and correlation with histology. Ultrasound Obstet Gynecol. 2011;37(4):471-479.
36. Exacoustos C, Manganaro L, Zupi E. Imaging for the evaluation of endometriosis and adenomyosis. Best Pract Res Clin Obstet Gynaecol. 2014;28(5):655-681.
37. Garcia L, Isaacson K. Adenomyosis: review of the literature. J Minim Invasive Gynecol. 2011;18(4):428-437.
38. Naftalin J, Hoo W, Nunes N, Holland T, Mavrelos D, Jurkovic D. Association between ultrasound features of adenomyosis and severity of menstrual pain. Ultrasound Obstet Gynecol. 2016;47(6):779-783.
39. Pinzauti S, Lazzeri L, Tosti C, et al. Transvaginal sonographic features of diffuse adenomyosis in 1830-year-old nulligravid women without endometriosis: association with symptoms. Ultrasound Obstet Gynecol. 2015;46(6):730-736.
40. Kil K, Chung JE, Pak HJ, et al. Usefulness of CA125 in the differential diagnosis of uterine adenomyosis and myoma. Eur J Obstet Gynecol Reprod Biol. 2015;185:131-135.
41. Streuli I, Santulli P, Chouzenoux S, Chapron C, Batteux F. Serum Osteopontin Levels Are Decreased in Focal Adenomyosis. Reprod Sci. 2016 Sep 27 pii: 1933719116669054. [Epub ahead of print].
42. Alabiso G, Alio L, Arena S, et al; Endometriosis Treatment Italian Club. Adenomyosis: What the Patient Needs. J Minim Invasive Gynecol. 2016;23(4):476-488.
43. Streuli I, Dubuisson J, Santulli P, de Ziegler D, Batteux F, Chapron C. An update on the pharmacological management of adenomyosis. Expert Opin Pharmacother. 2014;15(16):2347-2360.
44. Pontis A, DAlterio MN, Pirarba S, de Angelis C, Tinelli R, Angioni S. Adenomyosis: a systematic review of medical treatment. Gynecol Endocrinol. 2016;32(9):696-700.
45. Mais V, Angioni S, Cossu E, et al. Laparoscopic treatment of a cystic adenomyoma. Ital J Gynaecol Obstet. 2005;27:398-399.
46. Gordts S, Campo R, Brosens I. Hysteroscopic diagnosis and excision of myometrial cystic adenomyosis. Gynecol Surg. 2014;11(4):273-278.
47. Yang Z, Cao YD, Hu LN, Wang ZB. Feasibility of laparoscopic high-intensity focused ultrasound treatment for patients with uterine localized adenomyosis. Fertil Steril. 2009;91(6): 2338-2343.
48. Vercellini P, Viganò P, Somigliana E, Fedele L. Endometriosis: pathogenesis and treatment. Nat Rev Endocrinol. 2014;10(5): 261-275.
49. Farquhar C, Brosens I. Medical and surgical management of adenomyosis. Best Pract Res Clin Obstet Gynaecol. 2006;20(4): 603-616.
50. Luisi S, Ciani V, Pinzauti S, et al. Non-hormonal targets for the medical treatment of endometriosis. J Endometr Pelvic Pain Disord. 2012;4(2):85-92.
51. Wellington K, Wagstaff AJ. Tranexamic acid: a review of its use in the management of menorrhagia. Drugs. 2003;63(13): 1417-1433.
52. Lethaby A, Duckitt K, Farquhar C. Non-steroidal anti-inflammatory drugs for heavy menstrual bleeding. Cochrane Database Syst Rev. 2013;1(1):CD000400.
53. Ishihara H, Kitawaki J, Kado N, Koshiba H, Fushiki S, Honjo H. Gonadotropin-releasing hormone agonist and danazol normalize aromatase cytochrome P450 expression in eutopic endometrium from women with endometriosis, adenomyosis, or leiomyomas. Fertil Steril. 2003;79(Suppl 1):735-742.
54. Khan KN, Kitajima M, Hiraki K, et al. Changes in tissue inflammation, angiogenesis and apoptosis in endometriosis, adenomyosis and uterine myoma after GnRH agonist therapy. Hum Reprod. 2010;25(3):642-653.
55. Khan KN, Kitajima M, Hiraki K, et al. Cell proliferation effect of GnRH agonist on pathological lesions of women with endometriosis, adenomyosis and uterine myoma. Hum Reprod. 2010;25(11):2878-2890.
56. Khan KN, Kitajima M, Hiraki K, Fujishita A, Nakashima M, Masuzaki H. Decreased expression of human heat shock protein 70 in the endometria and pathological lesions of women with adenomyosis and uterine myoma after GnRH agonist therapy. Eur J Obstet Gynecol Reprod Biol. 2015;187:6-13.
57. Grow DR, Filer RB. Treatment of adenomyosis with long-term GnRH analogues: a case report. Obstet Gynecol. 1991;78(3 Pt 2):538-539.
58. Silva PD, Perkins HE, Schauberger CW. Live birth after treatment of severe adenomyosis with a gonadotropin-releasing hormone agonist. Fertil Steril. 1994;61(1):171-172.
59. Hirata JD, Moghissi KS, Ginsburg KA. Pregnancy after medical therapy of adenomyosis with a gonadotropin-releasing hormone agonist. Fertil Steril. 1993;59(2):444-445.
60. Lin J, Sun C, Zheng H. Gonadotropin-releasing hormone agonists and laparoscopy in the treatment of adenomyosis with infertility. Chin Med J (Engl). 2000;113(5):442-445.
61. Niu Z, Chen Q, Sun Y, Feng Y. Long-term pituitary downregulation before frozen embryo transfer could improve pregnancy outcomes in women with adenomyosis. Gynecol Endocrinol. 2013;29(12):1026-1030.
62. Fedele L, Bianchi S, Frontino G. Hormonal treatments for adenomyosis. Best Pract Res Clin Obstet Gynaecol. 2008;22(2):333-339.
63. Schweppe KW. The place of dydrogesterone in the treatment of endometriosis and adenomyosis. Maturitas. 2009;65(Suppl 1):S23-S27.
64. Lazzeri L, Luisi S, Petraglia F. Progestins for the treatment of endometriosis: an update. J Endometr Pelvic Pain Disord. 2010;2(4):169-181. Available from http://www.j-endometriosis.com/article/progestins-for-the-treatment-of-endometriosis--an-update-je-10-106. Accessed November 24, 2016.
65. Okada H, Okamoto R, Tsuzuki T, Tsuji S, Yasuda K, Kanzaki H. Progestins inhibit estradiol-induced vascular endothelial growth factor and stromal cell-derived factor 1 in human endometrial stromal cells. Fertil Steril. 2011;96(3):786-791.
66. Muneyyirci-Delale O, Chandrareddy A, Mankame S, Osei-Tutu N, Gizycki H. Norethindrone acetate in the medical management of adenomyosis. Pharmaceuticals (Basel). 2012;5(10): 1120-1127.
67. Hill JA, Barbieri RL, Anderson DJ. Immunosuppressive effects of danazol in vitro. Fertil Steril. 1987;48(3):414-418.
68. Braun DP, Gebel H, Dmowski WP. Effect of danazol in vitro and in vivo on monocyte-mediated enhancement of endometrial cell proliferation in women with endometriosis. Fertil Steril. 1994;62(1):89-95.
69. Mizutani T, Nishiyama S, Amakawa I, Watanabe A, Nakamuro K, Terada N. Danazol concentrations in ovary, uterus, and serum and their effect on the hypothalamic-pituitary-ovarian axis during vaginal administration of a danazol suppository. Fertil Steril. 1995;63(6):1184-1189.
70. Luisi S, Razzi S, Lazzeri L, Bocchi C, Severi FM, Petraglia F. Efficacy of vaginal danazol treatment in women with menorrhagia during fertile age. Fertil Steril. 2009;92(4):1351-1354.
71. Bahamondes L, Valeria Bahamondes M, Shulman LP. Non-contraceptive benefits of hormonal and intrauterine reversible contraceptive methods. Hum Reprod Update. 2015;21(5): 640-651.

72. Kauffman RP. Review: levonorgestrel IU system, OCPs, and antifibrinolytics each reduce bleeding in endometrial dysfunction. Ann Intern Med. 2013;159(6):JC10.
73. Yun BH, Jeon YE, Seo SK, et al. Effects of a Levonorgestrel-Releasing Intrauterine System on the Expression of Steroid Receptor Coregulators in Adenomyosis. Reprod Sci. 2015;22(12): 1539-1548.
74. Cho S, Choi YS, Yun BH, et al. Effects of levonorgestrel-releasing intrauterine system on lymphangiogenesis of adenomyosis. Am J Clin Pathol. 2015;143(3):352-361.
75. Fedele L, Bianchi S, Raffaelli R, Portuese A, Dorta M. Treatment of adenomyosis-associated menorrhagia with a levonorgestrel-releasing intrauterine device. Fertil Steril. 1997;68(3): 426-429.
76. Matteson KA, Rahn DD, Wheeler TL II, et al; Society of Gynecologic Surgeons Systematic Review Group. Nonsurgical management of heavy menstrual bleeding: a systematic review. Obstet Gynecol. 2013;121(3):632-643.
77. Shaaban OM, Ali MK, Sabra AM, Abd El Aal DE. Levonorgestrel-releasing intrauterine system versus a low-dose combined oral contraceptive for treatment of adenomyotic uteri: a randomized clinical trial. Contraception. 2015;92(4):301-307.
78. Petta CA, Ferriani RA, Abrao MS, et al. Randomized clinical trial of a levonorgestrel-releasing intrauterine system and a depot GnRH analogue for the treatment of chronic pelvic pain in women with endometriosis. Hum Reprod. 2005;20(7): 1993-1998.
79. Sheng J, Zhang WY, Zhang JP, Lu D. The LNG-IUS study on adenomyosis: a 3-year follow-up study on the efficacy and side effects of the use of levonorgestrel intrauterine system for the treatment of dysmenorrhea associated with adenomyosis. Contraception. 2009;79(3):189-193.
80. Ji F, Yang XH, Ai Xing Zi AL, Ha Ni Ke Zi TX, He Y, Ding Y. Role of levonorgestrel-releasing intrauterine system in dysmenorrhea due to adenomyosis and the influence on ovarian function. Clin Exp Obstet Gynecol. 2014;41(6):677-680.
81. Oettel M, Breitbarth H, Elger W, et al. The pharmacological profile of dienogest. Eur J Contracept Reprod Health Care. 1999; 4(sup1):2-13.
82. Foster RH, Wilde MI. Dienogest. Drugs. 1998;56(5):825-833, discussion 834-835.
83. Horie S, Harada T, Mitsunari M, Taniguchi F, Iwabe T, Terakawa N. Progesterone and progestational compounds attenuate tumor necrosis factor alpha-induced interleukin-8 production via nuclear factor kappa B inactivation in endometriotic stromal cells. Fertil Steril. 2005;83(5):1530-1535.
84. Yamanaka A, Kimura F, Kishi Y, et al. Progesterone and synthetic progestin, dienogest, induce apoptosis of human primary cultures of adenomyotic stromal cells. Eur J Obstet Gynecol Reprod Biol. 2014;179:170-174.
85. Fawzy M, Mesbah Y. Comparison of dienogest versus triptorelin acetate in premenopausal women with adenomyosis: a prospective clinical trial. Arch Gynecol Obstet. 2015;292(6): 1267-1271.
86. Hirata T, Izumi G, Takamura M, et al. Efficacy of dienogest in the treatment of symptomatic adenomyosis: a pilot study. Gynecol Endocrinol. 2014;30(10):726-729.
87. Maia H Jr, Casoy J, Correia T, et al. Effect of the menstrual cycle and oral contraceptives on aromatase and cyclooxygenase-2 expression in adenomyosis. Gynecol Endocrinol. 2006;22(10): 547-551.
88. Schindler AE. Hormonal contraceptives and endometriosis/adenomyosis. Gynecol Endocrinol. 2010;26(12):851-854.
89. Schindler AE. Non-contraceptive benefits of oral hormonal contraceptives. Int J Endocrinol Metab. 2013;11(1):41-47.
90. Chen YJ, Li HY, Huang CH, et al. Oestrogen-induced epithelial-mesenchymal transition of endometrial epithelial cells contributes to the development of adenomyosis. J Pathol. 2010;222(3):261-270.
91. Lee WL, Cheng MH, Chao HT, Wang PH. The role of selective estrogen receptor modulators on breast cancer: from tamoxifen to raloxifene. Taiwan J Obstet Gynecol. 2008;47(1):24-31.
92. Pinkerton JV, Thomas S. Use of SERMs for treatment in postmenopausal women. J Steroid Biochem Mol Biol. 2014;142: 142-154.
93. Taylor HS, Osteen KG, Bruner-Tran KL, et al. Novel therapies targeting endometriosis. Reprod Sci. 2011;18(9):814-823.
94. Bulun SE, Cheng YH, Pavone ME, et al. Estrogen receptor-beta, estrogen receptor-alpha, and progesterone resistance in endometriosis. Semin Reprod Med. 2010;28(1):36-43.
95. Bulun SE, Sebastian S, Takayama K, Suzuki T, Sasano H, Shozu M. The human CYP19 (aromatase P450) gene: update on physiologic roles and genomic organization of promoters. J Steroid Biochem Mol Biol. 2003;86(3-5):219-224.
96. Kitawaki J, Noguchi T, Amatsu T, et al. Expression of aromatase cytochrome P450 protein and messenger ribonucleic acid in human endometriotic and adenomyotic tissues but not in normal endometrium. Biol Reprod. 1997;57(3):514-519.
97. Badawy AM, Elnashar AM, Mosbah AA. Aromatase inhibitors or gonadotropin-releasing hormone agonists for the management of uterine adenomyosis: a randomized controlled trial. Acta Obstet Gynecol Scand. 2012;91(4):489-495.
98. Kimura F, Takahashi K, Takebayashi K, et al. Concomitant treatment of severe uterine adenomyosis in a premenopausal woman with an aromatase inhibitor and a gonadotropin-releasing hormone agonist. Fertil Steril. 2007;87(6):1468.e9-1468.e12.
99. Wagenfeld A, Saunders PT, Whitaker L, Critchley HO. Selective progesterone receptor modulators (SPRMs): progesterone receptor action, mode of action on the endometrium and treatment options in gynecological therapies. Expert Opin Ther Targets. 2016;20(9):1045-1054.
100. Kashani BN, Centini G, Morelli SS, Weiss G, Petraglia F. Role of medical management for uterine leiomyomas. Best Pract Res Clin Obstet Gynaecol 2015;34:85-103.
101. Angioni S, Cofelice V, Sedda F, et al. Progestins for symptomatic endometriosis: results of clinical studies. Current Drug Therapy. 2015;10(2):91-104.
102. Wang Y, Jiang X, Wang S. The influence of mifepristone to caspase 3 expression in adenomyosis. Clin Exp Obstet Gynecol. 2014;41(2):154-157.
103. Li Y, Zhang SF, Zou SE, Xia X, Bao L. Accumulation of nerve growth factor and its receptors in the uterus and dorsal root ganglia in a mouse model of adenomyosis. Reprod Biol Endocrinol. 2011;9(1):30.
104. Li Y, Zou S, Xia X, Zhang S. Human adenomyosis endometrium stromal cells secreting more nerve growth factor: impact and effect. Reprod Sci. 2015;22(9):1073-1082.
105. Li B, Chen M, Liu X, Guo SW. Constitutive and tumor necrosis factor-α-induced activation of nuclear factor-κB in adenomyosis and its inhibition by andrographolide. Fertil Steril. 2013;100(2): 568-577.
106. Wang F, Li H, Yang Z, Du X, Cui M, Wen Z. Expression of interleukin-10 in patients with adenomyosis. Fertil Steril. 2009;91(5): 1681-1685.
107. Tokyol C, Aktepe F, Dilek FH, Sahin O, Arioz DT. Expression of cyclooxygenase-2 and matrix metalloproteinase-2 in adenomyosis and endometrial polyps and its correlation with angiogenesis. Int J Gynecol Pathol. 2009;28(2):148-156.
108. Pinkerton JV. Pharmacological therapy for abnormal uterine bleeding. Menopause. 2011;18(4):453-461.