Role of medical therapy in the management of uterine adenomyosis

Role of medical therapy in the management of uterine adenomyosis

Silvia Vannuccini, M.D.,[a] Stefano Luisi, M.D., Ph.D.,[b] Claudia Tosti, M.D.,[b] Flavia Sorbi, M.D.,[c] and Felice Petraglia, M.D.[c]

[a] Department of Health Sciences, University of Florence, Obstetrics and Gynecology, Careggi University Hospital, Florence; [b] Department of Molecular and Developmental Medicine, University of Siena, Siena; and [c] Department of Experimental, Clinical and Biomedical Sciences, University of Florence, Obstetrics and Gynecology, Careggi University Hospital, Florence, Italy

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.)
Key Words: Adenomyosis, GnRH analogues, levonorgestrel-IUS, medical therapy, progestins

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.

Received December 12, 2017; revised January 8, 2018; accepted January 9, 2018.
S.V. has nothing to disclose. S.L. has nothing to disclose. C.T. has nothing to disclose. F.S. has nothing to disclose. F.P. has nothing to disclose.
Correspondence: Felice Petraglia, M.D., Obstetrics and Gynecology, Department of Experimental, Clinical and Biomedical Sciences, University of Florence, Largo Brambilla 3, Florence 50134, Italy (E-mail: felice.petraglia@unifi.it).

Fertility and Sterility® Vol. 109, No. 3, March 2018 0015-0282/$36.00

https://doi.org/10.1016/j.fertnstert.2018.01.013

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.

Vannuccini. Medical management of adenomyosis. Fertil Steril 2018.

cells (25), reducing bleeding and pain. In addition, progestins may act on the progesterone resistance observed in ectopic and eutopic endometrium, but also in the inner and outer layers of the myometrium adenomyosis (13) (Table 1).

An effect of NETA in the management of adenomyosis has been demonstrated in women with moderate or severe pelvic pain and bleeding, obtaining a significant improvement of both dysmenorrhea and bleeding after treatment (5 mg/d dose) (26) (Table 1). In this treatment group, the 'three weeks on, one week off' regime was adopted to minimize the common side effect of breakthrough bleeding, causing an incomplete suppression of the hypothalamic-pituitary-ovarian axis and a less hypoestrogenic effect. According to these results, NETA may be considered an effective, well-tolerated and inexpensive medical treatment for adenomyosis, with few and mild side effects. However, no further studies have been conducted comparing NETA to other progestins or other drug, and no evidences are available on long term effects on symptoms and sonographic or magnetic resonance imaging appearance of adenomyosis after discontinuation of NETA treatment.

Danazol

Danazol, an isoxazole derivative of 12 aloha-ethinyl testosterone, has strong antigonadotropic properties (27), lowering the mid-cycle luteinizing hormone surge and increasing serum free testosterone levels (28). The androgenic and hypoestrogenic milieu cause both a direct effect on adenomyotic lesions and an indirect effect on symtoms (29). Studies in vitro showed danazol has a direct effect on cell proliferation, by inhibiting DNA synthesis and inducing apoptosis. Glands and stromal cells of adenomyosis analyzed after systemic treatment with danazol show a reduction in estrogen receptor and bcl-2 protein concentrations, with an increase in apoptotic cell necrosis (30). Danazol also inhibits lymphocyte proliferation, reduces monocyte-enhanced endometrial proliferation in peripheral blood and increases peritoneal macrophage cytotoxicity (31, 32). The study by Ota et al. (33), the only randomized controlled trial on danazol, compared hysterectomy versus a 4 month treatment with 400 mg of daily danazol; post-treatment autoantibody levels and antiphospholipid levels were decreased, due to the inhibitory effect of danazol on the autoimmunological response associated with adenomyosis.

Limited evidence is available on systemic treatment of adenomyosis with danazol, due to the high incidence of androgenic side effects. The first to use danazol to treat adenomyosis in a different route than the systemic one was Igarashi who used an intrauterine device containing 175 mg of danazol. The treatment resulted effective in reducing the size of the uterus and pregnancy was achieved in 66.6% cases (34). Cervical injections of danazol at 2 week intervals for 12 weeks have also been successfully used, with 60% improvement in symptoms of bleeding, pain, and dyspareunia, and a decrease in uterine size (35). Also an intrauterine device loaded with 300 mg–400 mg of danazol caused a great reduction of pain symptoms. During the treatment, blood danazol levels were undetectable, ovulation was not inhibited, and no side effects were reported (36). The same device loaded with danazol was used in a murine model, and it was observed that as the danazol dose increased, the adenomyotic nodule number decreased, with a low and stable plasma danazol concentration (37).

A prospective study showed long-term vaginal administration of one 200 mg danazol tablet every day is effective in reducing heavy menstrual bleeding and pain in adenomyotic women (38) (Table 1). Recently, it was observed that a long-term treatment with vaginal danazol can control pain and AUB in women with adenomyosis. There was an improvement in visual analogue scale score for pain symptoms, pictorial blood-loss assessment chart for uterine bleeding and quality-of-life measures, with a reduction of uterine volume evaluated by ultrasound. The 6-month treatment followed by a cyclic 3-month treatment for a further 18 months had the best compliance in symptomatic patients with adenomyosis (39).

The positive changes induced by danazol were markedly increased compared with leuprolide acetate, although, even after 6 months of therapy, menorrhagia and dysmenorrhea recurred within a few cycles of treatment suspension of danazol (30).

Dienogest

Dienogest (DNG), a 19-nortestosterone derivative, is a progestin with high selectivity for progesterone receptors (40). It causes a mild inhibition of ovarian function, with slight hypoestrogenic effects, and it exerts an antiproliferative action on the endometrium (41). Cellular proliferation of adenomyotic cells is inhibited also by inducing apoptotic pathways (42). In addition, uterine samples taken after hysterectomy from women treated with DNG showed significant changes in histological features, such as reduction in cell proliferation, nerve growth factor expression and nerve fiber density (21). These findings support the clinical evidences that DNG is effective in treating adenomyosis-associated pain symptoms (Table 1). On the basis of significant changes in the immune system, with an increased number of uterine infiltrating natural killer cells in glandular structure of eutopic endometrium, a potential beneficial effect on embryo implantation has also been hypothesized (43).

The first pilot study on DNG was conducted in seventeen premenopausal women with symptomatic adenomyosis and the drug resulted effective in improving the pain symptoms, although some of them experienced more frequent menorrhagia with worsening of anemia (44). A randomized, double-blind, multicenter, and placebo-controlled trial on DNG, daily administered for 16 weeks in women with adenomyosis, showed a significant decrease of pain score and visual analogue scale between DNG and placebo (45). A greater reduction of uterine volume in the DNG group was observed, without reaching significance. The drug was well-tolerated, although a high portion of women reported irregular uterine bleeding during treatment.

Another recent study from the same group evaluated safety and efficacy of long-term administration of DNG (52 weeks) (46). DNG resulted effective in reducing pain-score scale for dysmenorrhea and pelvic pain and in

decreasing the need for analgesics. Pain score significantly decreased after 24 and 52 weeks of treatment improving patients' quality of life. In fact, the Bodily Pain subscale score in SF-36 was almost the same for the general population. The most common adverse drug reactions included metrorrhagia (96.9%) and hot flush (7.7%), but in most cases the bleeding, due to the progestational action of DNG on the endometrium, was tolerable. However, a retrospective study (on 51 patients) showed that young age and anemia prior to treatment were risk factors for cessation of treatment with DNG (47).

The comparison between DNG and GnRH analogues showed no difference in terms of pelvic pain reduction, as both were effective in pain control. However, four months of treatment with GnRH analogues induced a greater reduction of AUB symptoms and uterine volume evaluated by ultrasound (48).

Levonorgestrel-releasing Intrauterine System

Levonorgestrel-releasing intrauterine system (LNG-IUS) has been successfully used to treat adenomyosis with the aim to reduce menstrual blood loss and pain via a reduction in thickness of the myometrial junctional zone and total uterine volume (49–51) (Table 1). LNG-IUS is effective in reducing menstrual bleeding, even in women without adenomyosis and is inserted for contraceptive needs (52). The reduction of menstrual blood loss is attributed to both direct effect of levonorgestrel on adenomyosis foci with decidualization and increase in apoptosis in endometrial glands and stroma (53). In fact, local levonorgestrel release caused atrophy and shrinkage of adenomyotic lesions through a downregulation of estrogen receptors, preventing further stimulation by estrogens (54). The LNG-IUS guarantees reduction in side effects caused by other oral treatment providing, in contrast with relatively low serum levels, locally high concentrations of LNG in the endometrium and adjacent tissues.

LNG-IUS is an effective and simple alternative method for the treatment of chronic pelvic pain. This is a cost effective, reversible, and long-term treatment for women with pelvic pain associated with adenomyosis, especially mild and moderately severe (55), reducing the need for surgical interventions.

In women treated with LNG-IUS for 3 years there was an overall satisfaction of 72%, with continued significant decrease in dysmenorrhea and uterine volume compared to baseline (56). Even though pain reduction improves quite rapidly, uterine volume reduction may not occur until 2 years post insertion (57). LNG-IUS action towards bleeding is mediated by a reduction in Vascular endothelial growth factor, endometrial levels (58). A randomized controlled-trial on 75 women undergoing either LNG-IUS or hysterectomy showed that 6 months post treatment hemoglobin levels were comparable and quality of life increased with LNG-IUS versus hysterectomy (59).

LNG-IUS showed effective in reduction of urinary symptoms at 6 months post treatment and improvement in incontinence in 65 women with sonographic adenomyosis prospectively enrolled (60). Zhang et al. (61) performed a prospective study on 21 women with a uterine size of <12 weeks gestation treated with GnRH analogues until uterine size reduction <10 weeks gestation. Then LNG-IUS was inserted, and after 12 months of combined treatment, women had significantly reduced menstrual bleeding and dysmenorrhea, with a reduced uterine size, and a low LNG-IUS expulsion rate.

A randomized clinical trial comparing combined oral contraceptives (COCs) vs LNG-IUS showed both reduced pain and menstrual loss, but the intrauterine device is more effective in these outcomes (62). To date, the cutoff value of uterine volume more than 150 mL was significantly associated with failure of LNG-IUS, thus the insertion of an LNG-IUS in a large volume uterus has a significantly higher failure rate than that of a small volume uterus (63).

COMBINED ORAL CONTRACEPTIVES

The rationale for using COCs in adenomyosis is related to the induced decidualization and subsequent atrophy of the endometrium, reducing pain and AUB (Table 1). Patients with dysmenorrhea and menorrhagia in fact may benefit from the resulting amenorrhea, which may provide relief of symptoms (64). In addition, COCs suppress aromatase expression in the eutopic endometrium and in adenomyotic foci (65). Despite the common off-label use of COCs for adenomyosis-related symptoms with satisfactory long-term pain control, no well conducted randomized controlled trials are available supporting the pharmacological treatment of adenomyosis using COCs.

NON-STEROIDAL ANTI-INFLAMMATORY DRUGS

Non-steroidal anti-inflammatory drugs (NSAIDs) are non-hormonal compounds commonly used as a symptomatic treatment for dysmenorrhea and heavy bleeding associated with adenomyosis (Table 1). A systematic review showed that they are effective in treating menstrual pain, without indicating which drug is the most appropriate and the safest for this purpose (66). Another systematic review reported that NSAIDs may be used for reducing menstrual bleeding, even though they are less effective than hormonal treatment or tranexamic acid (67). However, no specific studies on the use of NSAIDs in adenomyosis are currently available.

NOVEL DRUGS UNDER INVESTIGATION

Aromatase Inhibitors

Aromatase cytochrome P450 (CYP19A1), a key enzyme in the synthesis of estrogen from androgens, is typically found in the endometrium of women with endometriosis, adenomyosis and leiomyomas, but not in that of healthy women (68, 69). This enzyme is involved in the conversion of androstenedione and testosterone to estrone and estradiol, respectively. The first documented use of aromatase inhibitors (AIs) in adenomyosis was reported in a woman with severe adenomyosis refractory to GnRH analogues and danazol, who wished to preserve her fertility. Anastrozole was administered orally for 16 weeks, in combination with

GnRH analogues, to suppress the ovarian production of estrogens. Reduction of uterine volume was 60% after 8 weeks of treatment and the patient had no AUB for 6 months after cessation of AI administration (70). Results from a randomized controlled-trial comparing a treatment for 3 months with an aromatase inhibitor (letrozole 2.5 mg/d) and goserelin 3.6 mg monthly showed that AIs have the same efficacy as GnRH analogues in reducing adenomyoma volume and improving symptoms. In fact in both treatments a significant difference in uterine volume after 3 months was observed, without a relevant change in adenomyotic area (41% vs. 49%) at study completion (71). AIs seems to have a promising future for adenomyosis in cases of resistance to other treatments even though additional studies are needed (6).

Selective Progesterone Receptor Modulators

The progesterone receptors play an essential role in uterine physiology and reproduction. Selective progesterone receptor modulators (SPRMs) have emerged as a valuable treatment option for hormone dependent conditions like uterine fibroids (72). SPRMs exhibit progesterone agonist and antagonist activities in the endometrium, reducing pain, bleeding, cell proliferation and inhibiting inflammation (73, 74), thus they may be a promising treatment for endometriosis and adenomyosis as well. Previous evidences on mifepristone showed that it influences the caspase 3 expression in adenomyosis tissue, inducing cell apoptosis, inhibiting the onset and development of adenomyosis (75). However, only a few small clinical studies on endometriosis showed the potential application of SPRMs in adenomyosis. The administration of mifepristone 50-mg daily improved pain and caused regression of endometriotic lesions (76). Similarly, asoprisnil and telapristone acetate have also been reported to relieve endometriosis-associated pain (77). However, SPRMs require investigations and well designed, randomized controlled trials to assess their long-term effects and their clinical use in patients with adenomyosis. A phase II, randomized, double-blind, controlled trial with ulipristal acetate 10 mg/day for 3 months in patients with adenomyosis wishing to keep fertility has just been registered. The primary outcome is to evaluate the efficiency of ulipristal acetate on bleeding control and pain in adenomyosis.

GnRH Antagonists

GnRH-antagonists (GnRH-ant) are peptide compounds with a structure similar to natural GnRH that inhibit the reproductive system through an immediate antagonist action on GnRH receptors in the pituitary, blocking the secretion of gonadotropins. They are usually used in antagonist stimulation protocols in ART. Recently, two double-blind, randomized, phase 3 trials on women with endometriosis treated with different doses of elagolix, an oral nonpeptide GnRH-ant, were published (78). Both schedules of elagolix were effective in improving dysmenorrhea and nonmenstrual pelvic pain during a 6-month period in women with moderate to severe endometriosis-associated pain (78) The mechanism of action of GnRH-ant is different from that of GnRH analogues which after an initial stimulatory phase desensitize GnRH receptors in the pituitary and subsequently cause depletion of pituitary gonadotropins and full suppression of estradiol. GnRH-ant do not induce neither downregulation nor desensitization of the receptors, as they act competitively preventing endogenous GnRH from binding and activating its pituitary receptor. Thus, depending on the dose of antagonist administered, the estradiol suppression can be modulated. The treatment may partially suppress estradiol without having to administer add-back therapy, or fully suppress estradiol when combined with add-back therapy (79). Considering the promising results of GnRH-ant in endometriosis, a future use for treating adenomyosis-related symptoms may be hypothesized.

Valproic Acid

Increasing evidence is showing that adenomyosis is an epigenetic disease (13). Class I histone deacetylases seem to be involved in the pathogenesis, as their expression has been found to be increased in eutopic and ectopic endometrium in adenomyosis, correlating with severity of dysmenorrhea (80). Valproic acid (VPA), a specific and potent histone deacetylase inhibitor, used for decades for treating epilepsy, has been shown to be effective in treating a small series of women with adenomyosis, decreasing dysmenorrhea and uterine bleeding, and reducing the uterus size (81, 82). Studies on murine models of adenomyosis showed the mechanism of action of VPA, that suppressed myometrial infiltration, improved generalized hyperalgesia, and reduced the amplitude and irregularity of uterine contractions (83, 84). Despite these promising results in favor of the use of histone deacetylase inhibitors, so far no clinical trials have been conducted to evaluate the efficacy of VPA in adenomyosis.

Anti-platelet Therapy

Emerging evidence supports an important role of platelets in adenomyosis pathogenesis, according to the theory that adenomyotic lesions are wounds undergoing repeated tissue injury and repair (85). Platelets induce epithelial-mesenchymal transition, fibroblast-to-myofibroblast transdifferentiation, leading ultimately to fibrosis (86). A recent study in a mouse model of adenomyosis demonstrated that anti-platelet treatment (thromboxane A2 synthese inhibitor) is efficacious in suppressing myometrial infiltration, improving generalized hyperalgesia, reducing both uterine hyperactivity and systemic corticosterone levels. In addition, a decreased expression of some proteins involved in adenomyosis fibrogenesis was demonstrated, supporting the promising role of anti-platelets therapy in adenomyosis (87). However, so far there are currently no studies published or registered on the use of agents targeting platelets.

MEDICAL TREATMENT IN INFERTILE WOMEN WITH ADENOMYOSIS

The presence of adenomyosis is diagnosed in a higher frequency in patients consulting with fertility problems, with a prevalence ranging from 20%–25% in women undergoing ART (10). A dysregulation of the myometrial structure and

an altered endometrial function contributes to the negative impact of adenomyosis on fertility (88, 89). However, there is no agreement on the most appropriate therapeutic methods for managing women with adenomyosis trying to conceive. A number of studies have shown that GnRH treatment may improve the reproductive performance, possibly promoting uterine and endometrial receptivity (90). The first case reports on the use of GnRH analogues showed that after a 6-month treatment with nafarelin acetate or a 5-month treatment with leuprolide acetate respectively, two women with severe adenomyosis spontaneously conceived (91, 92). The use of GnRH analogues was tested also both before and after surgical treatment for adenomyosis, with relatively good results for fertility, even though only small series or case reports supported this management (90, 93, 94). Some studies have shown that administration of GnRH analogues before in vitro fertilization (IVF) cycles significantly increases the chances of pregnancy in infertile women with adenomyosis or endometriosis (95–97). Niu et al. (98) demonstrated that long-term GnRH agonist pretreatment improves pregnancy outcomes in adenomyosis patients undergoing frozen embryo transfer (FET) after preparation of the endometrium with hormone replacement therapy (98). Another recent retrospective study was conducted on 241 infertile women with adenomyosis diagnosed by ultrasound undergoing IVF and fresh embryo transfer (ET) cycles or FET cycles. Results showed no difference between cases with or without GnRH analogues pretreatment with goserelin for 2-3 months in a large number of fresh ET cycles, indicating that GnRH analogues pretreatment has no benefit in improving IVF outcomes in these cases. On the contrary, a higher clinical pregnancy rate was observed in women undergoing FET cycles after GnRH pretreatment (39.5%) than those undergoing to fresh ET with (30.5%) or without (25.2%) GnRH analogues pretreatment (99).

A very recent systematic review and meta-analysis summarized the existing evidence related to the effect of adenomyosis on fertility and on IVF clinical outcomes, showing that pretreatment with the use of long-term GnRH analogues or long protocol could be beneficial in increasing the clinical pregnancy rate, both in symptomatic and asymptomatic patients (100). Adenomyosis has a detrimental effect on IVF clinical outcomes, reducing pregnancy and live birth rates and increases the miscarriage rate. Pre-IVF treatment with the use of GnRH analogues down-regulation may be beneficial, but further studies are needed (100).

CONCLUSIONS

Medical treatment plays an important role in the management of adenomyosis, especially in diffuse forms and in those women requiring preservation or restoration of fertility. Medical management is a valid choice for treating pain symptoms and bleeding, resulting very frequently in a more acceptable option than surgical treatment. So far, no labelled drugs are available, however those commonly used are effective in managing symptoms and improving pregnancy rate in ART.

Randomized clinical studies are needed to systematically test the clinical usefulness of drugs commonly used and identify the most effective ones. In addition, on the basis of the new discoveries on pathogenetic mechanisms of adenomyosis, the introduction of new molecules is desirable.

REFERENCES

1. Abbott JA. Adenomyosis and Abnormal Uterine Bleeding (AUB-A)—Pathogenesis, diagnosis, and management. Best Pract Res Clin Obstet Gynaecol 2017;40:68–81.
2. Exacoustos C, Luciano D, Corbett B, De Felice G, Di Feliciantonio M, Luciano A, et al. The uterine junctional zone: A 3-dimensional ultrasound study of patients with endometriosis. Am J Obstet Gynecol 2013;209:248.e1–7.
3. Exacoustos C, Manganaro L, Zupi E. Imaging for the evaluation of endometriosis and adenomyosis. Best Pract Res Clin Obstet Gynaecol 2014;28:655–81.
4. Van Den Bosch T, Dueholm M, Leone FPG, Valentin L, Rasmussen CK, Votino A, et al. Terms, definitions and measurements to describe sonographic features of myometrium and uterine masses: A consensus opinion from the Morphological Uterus Sonographic Assessment (MUSA) group. Ultrasound Obstet Gynecol 2015;46:284–98.
5. Peric H, Fraser IS. The symptomatology of adenomyosis. Best Pract Res Clin Obstet Gynaecol 2006;20:547–55.
6. Tosti C, Troìa L, Vannuccini S, Lazzeri L, Luisi S, Petraglia F. Current and future medical treatment of adenomyosis. J Endometr 2016;8:127–35.
7. Pinzauti S, Lazzeri L, Tosti C, Centini G, Orlandini C, Luisi S, et al. Transvaginal sonographic features of diffuse adenomyosis in 18-30-year-old nulligravid women without endometriosis: Association with symptoms. Ultrasound Obstet Gynecol 2015;46:730–6.
8. Naftalin J, Hoo W, Pateman K, Mavrelos D, Holland T, Jurkovic D. How common is adenomyosis? A prospective study of prevalence using transvaginal ultrasound in a gynaecology clinic. Hum Reprod 2012;27:3432–9.
9. Chapron C, Tosti C, Marcellin L, Bourdon M, Lafay-Pillet MC, Millischer AE, et al. Relationship between the magnetic resonance imaging appearance of adenomyosis and endometriosis phenotypes. Hum Reprod 2017;32:1393–401.
10. Puente JM, Fabris A, Patel J, Patel A, Cerrillo M, Requena A, et al. Adenomyosis in infertile women: prevalence and the role of 3D ultrasound as a marker of severity of the disease. Reprod Biol Endocrinol 2016;14:60.
11. Taran FA, Weaver AL, Coddington CC, Stewart EA. Characteristics indicating adenomyosis coexisting with leiomyomas: A case-control study. Hum Reprod 2010;25:1177–82.
12. Lazzeri L, Di Giovanni A, Exacoustos C, Tosti C, Pinzauti S, Malzoni M, et al. Preoperative and Postoperative Clinical and Transvaginal Ultrasound Findings of Adenomyosis in Patients With Deep Infiltrating Endometriosis. Reprod Sci 2014;21:1027–33.
13. Vannuccini S, Tosti C, Carmona F, Huang SJ, Chapron C, Guo SW, et al. Pathogenesis of adenomyosis: An update on molecular mechanisms. Reprod Biomed Online 2017;35:592–601.
14. Fedele L, Bianchi S, Frontino G. Hormonal treatments for adenomyosis. Best Pract Res Clin Obstet Gynaecol 2008;22:333–9.
15. Pontis A, D'Alterio MN, Pirarba S, de Angelis C, Tinelli R, Angioni S. Adenomyosis: a systematic review of medical treatment. Gynecol Endocrinol 2016;3590:1–5.
16. Khan KN, Kitajima M, Hiraki K, Fujishita A, Nakashima M, Ishimaru T, et al. Cell proliferation effect of GnRH agonist on pathological lesions of women with endometriosis, adenomyosis and uterine myoma. Hum Reprod 2010;25:2878–90.
17. 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(3 Suppl. 1):735–42.
18. Khan KN, Kitajima M, Hiraki K, Fujishita A, Sekine I, Ishimaru T, et al. Changes in tissue inflammation, angiogenesis and apoptosis in endometriosis, adenomyosis and uterine myoma after GnRH agonist therapy. Hum Reprod 2010;25:642–53.

19. Kamada Y, Nakatsuka M, Asagiri K, Noguchi S, Habara T, Takata M, et al. GnRH agonist-suppressed expression of nitric oxide synthases and generation of peroxynitrite in adenomyosis. Hum Reprod 2000;15:2512–9.
20. Grow DR, Filer RB. Treatment of adenomyosis with long-term GnRH analogues: A case report. Obstet Gynecol 1991;78:538–9.
21. Takeuchi A, Koga K, Miyashita M, Makabe T, Sue F, Harada M, et al. Dienogest reduces proliferation, NGF expression and nerve fiber density in human adenomyosis. Eur J Obstet Gynecol Reprod Biol 2016;207:157–61.
22. Nelson JR, Corson SL. Long-term management of adenomyosis with a gonadotropin-releasing hormone agonist: A case report. Fertil Steril 1993;59:441–3.
23. 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;15:2347–60.
24. Akira S, Mine K, Kuwabara Y, Takeshita T. Efficacy of long-term, low-dose gonadotropin-releasing hormone agonist therapy (draw-back therapy) for adenomyosis. Med Sci Monit 2009;15:CR1–4.
25. 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;96:786–91.
26. Muneyyirci-Delale O, Chandrareddy A, Mankame S, Osei-Tutu N, von Gizycki H. Norethindrone acetate in the medical management of adenomyosis. Pharmaceuticals 2012;5:1120–7.
27. Lauersen NH, Wilson KH, Birnbaum S. Danazol: an antigonadotropic agent in the treatment of pelvic endometriosis. Am J Obstet Gynecol 1975;123:742–7.
28. Barbieri RL. Danazol: molecular, endocrine, and clinical pharmacology. Prog Clin Biol Res 1990;323:241–52.
29. Beaumont H, Augood C, Duckitt K, Lethaby A. Danazol for heavy menstrual bleeding. Cochrane Database Syst Rev 2002:CD001017.
30. Ueki K, Kumagai K, Yamashita H, Li ZL, Ueki M, Otsuki Y. Expression of apoptosis-related proteins in adenomyotic uteri treated with danazol and GnRH agonists. Int J Gynecol Pathol 2004;23:248–58.
31. Hill JA, Barbieri RL, Anderson DJ. Immunosuppressive effects of danazol in vitro. Fertil Steril 1987;48:414–8.
32. 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;62:89–95.
33. Ota H, Maki M, Shidara Y, Kodama H, Takahashi H, Hayakawa M, et al. Effects of danazol at the immunologic level in patients with adenomyosis, with special reference to autoantibodies: a multi-center cooperative study. Am J Obstet Gynecol 1992;167:418–26.
34. Igarashi M. A New Therapy for Pelvic Endometriosis and Uterine Adenomyosis: Local Effect of Vaginal and Intrauterine Danazol Application. Asia Oceania J Obstet Gynaecol 1990;16:1–12.
35. Takebayashi T, Fujino Y, Umesaki N, Ogita S. Danazol suspension injected into the uterine cervix of patients with adenomyosis and myoma. Preliminary study. Gynecol Obstet Investig 1995;39:207–11.
36. Igarashi M, Abe Y, Fukuda M, Ando A, Miyasaka M, Yoshida M. Novel conservative medical therapy for uterine adenomyosis with a danazol-loaded intrauterine device. Fertil Steril 2000;74:412–3.
37. Zhang X, Yuan H, Deng L, Hu F, Ma J, Lin J. Evaluation of the efficacy of a danazol-loaded intrauterine contraceptive device on adenomyosis in an ICR mouse model. Hum Reprod 2008;23:2024–30.
38. 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;92:1351–4.
39. Tosti C, Vannuccini S, Troìa L, Luisi S, Centini G, Lazzeri L, et al. Long-term vaginal danazol treatment in fertile age women with adenomyosis. J Endometr Pelvic Pain Disord 2017;9:39–43.
40. Sasagawa S, Shimizu Y, Kami H, Takeuchi T, Mita S, Imada K, et al. Dienogest is a selective progesterone receptor agonist in transactivation analysis with potent oral endometrial activity due to its efficient pharmacokinetic profile. Steroids 2008;73:222–31.
41. Moore C, Carol W, Gräser T, Mellinger U, Walter F. Influence of dienogest on ovulation in young fertile women. Clin Drug Investig 1999;18:271–8.
42. Yamanaka A, Kimura F, Kishi Y, Takahashi K, Suginami H, Shimizu 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;179:170–4.
43. Prathoomthong S, Tingthanatikul Y, Lertvikool S, Rodratn N, Waiyaput W, Dittharot K, et al. The Effects of Dienogest on Macrophage and Natural Killer Cells in Adenomyosis: A Randomized Controlled Study. Int J Fertil Steril 2018;11:279–86.
44. Hirata T, Izumi G, Takamura M, Saito A, Nakazawa A, Harada M, et al. Efficacy of dienogest in the treatment of symptomatic adenomyosis: a pilot study. Gynecol Endocrinol 2014;30:726–9.
45. Osuga Y, Fujimoto-Okabe H, Hagino A. Evaluation of the efficacy and safety of dienogest in the treatment of painful symptoms in patients with adenomyosis: a randomized, double-blind, multicenter, placebo-controlled study. Fertil Steril 2017;108:673–8.
46. Osuga Y, Watanabe M, Hagino A. Long-term use of dienogest in the treatment of painful symptoms in adenomyosis. J Obstet Gynaecol Res 2017;43:1441–8.
47. Nagata C, Yanagida S, Okamoto A, Morikawa A, Sugimoto K, Okamoto S, et al. Risk factors of treatment discontinuation due to uterine bleeding in adenomyosis patients treated with dienogest. J Obstet Gynaecol Res 2012;38:639–44.
48. Fawzy M, Mesbah Y. Comparison of dienogest versus triptorelin acetate in premenopausal women with adenomyosis: a prospective clinical trial. Arch Gynecol Obstet 2015;292:1267–71.
49. Fraser IS. Non-contraceptive health benefits of intrauterine hormonal systems. Contraception 2010;82:396–403.
50. Sabbioni L, Petraglia F, Luisi S. Non-contraceptive benefits of intrauterine levonorgestrel administration: why not? Gynecol Endocrinol 2017;33:822–9.
51. Fedele L, Portuese A, Bianchi S, Dorta M, Raffaelli R. Treatment of adenomyosis-associated menorrhagia with a levonorgestrel- releasing intrauterine device. Fertil Steril 1997;68:426–9.
52. Kelekci S, Kelekci KH, Yilmaz B. Effects of levonorgestrel-releasing intrauterine system and T380A intrauterine copper device on dysmenorrhea and days of bleeding in women with and without adenomyosis. Contraception 2012;86:458–63.
53. Maruo T, Laoag-Fernandez JB, Pakarinen P, Murakoshi H, Spitz IM, Johansson E. Effects of the levonorgestrel-releasing intrauterine system on proliferation and apoptosis in the endometrium. Hum Reprod 2001;16:2103–8.
54. Critchley HOD, Wang H, Kelly RW, Gebbie AE, Glasier AF. Progestin receptor isoforms and prostaglandin dehydrogenase in the endometrium of women using a levonorgestrel-releasing intrauterine system. Hum Reprod 1998;13:1210–7.
55. Radzinsky VE, Khamoshina MB, Nosenko EN, Dukhin AO, Sojunov MA, Orazmuradov AA, et al. Treatment strategies for pelvic pain associated with adenomyosis. Gynecol Endocrinol 2016;32(sup2):19–22.
56. 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;79:189–93.
57. Cho S, Nam A, Kim H, Chay D, Park K, Cho DJ, et al. Clinical effects of the levonorgestrel-releasing intrauterine device in patients with adenomyosis. Am J Obstet Gynecol 2008;198:373.e1–7.
58. Laoag-Fernandez JB, Maruo T, Pakarinen P, Spitz IM, Johansson E. Effects of levonorgestrel-releasing intra-uterine system on the expression of vascular endothelial growth factor and adrenomedullin in the endometrium in adenomyosis. Hum Reprod 2003;18:694–9.
59. Ozdegirmenci O, Kayikcioglu F, Akgul MA, Kaplan M, Karcaaltincaba M, Haberal A, et al. Comparison of levonorgestrel intrauterine system versus hysterectomy on efficacy and quality of life in patients with adenomyosis. Fertil Steril 2011;95:497–502.
60. Ekin M, Cengiz H, Ayağ ME, Kaya C, Yasar L, Savan K. Effects of the levonorgestrel-releasing intrauterine system on urinary symptoms in patients with adenomyosis. Eur J Obstet Gynecol Reprod Biol 2013;170:517–20.

61. Zhang P, Song K, Li L, Yukuwa K, Kong B. Efficacy of combined levonorgestrel-releasing intrauterine system with gonadotropin-releasing hormone analog for the treatment of adenomyosis. Med Princ Pract 2013;22:480–3.
62. 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):301–7.
63. Lee KH, Kim JK, Lee MA, Ko YB, Yang JB, Kang BH, et al. Relationship between uterine volume and discontinuation of treatment with levonorgestrel-releasing intrauterine devices in patients with adenomyosis. Arch Gynecol Obstet 2016;294:561–6.
64. Schindler AE. Non-contraceptive use of hormonal contraceptives. Gynecol Endocrinol 2008;24:235–6.
65. Maia H, Casoy J, Correia T, Freitas L, Pimentel K, Athayde C, et al. Effect of the menstrual cycle and oral contraceptives on aromatase and cyclooxygenase-2 expression in adenomyosis. Gynecol Endocrinol 2006; 22:547–51.
66. Marjoribanks J, Ayeleke R, Farquhar C, Proctor M. Nonsteroidal anti-inflammatory drugs for dysmenorrhoea. Cochrane Database Syst Rev 2015:CD001751.
67. Lethaby A, Duckitt K, Farquhar C. Non-steroidal anti-inflammatory drugs for heavy menstrual bleeding. Cochrane Database Syst Rev 2013;1: CD000400.
68. Kitawaki J, Noguchi T, Amatsu T, Maeda K, Tsukamoto K, Yamamoto 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;57:514–9.
69. Yamamoto T, Noguchi T, Tamura T, Kitawaki J, Okada H. Evidence for estrogen synthesis in adenomyotic tissues. Am J Obstet Gynecol 1993;169: 734–8.
70. Kimura F, Takahashi K, Takebayashi K, Fujiwara M, Kita N, Noda Y, 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;87:1468.e9–12.
71. 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;91:489–95.
72. Whitaker LHR, Williams ARW, Critchley HOD. Selective progesterone receptor modulators. Curr Opin Obstet Gynecol 2014;26:237–42.
73. Wagenfeld A, Saunders PTK, Whitaker L, Critchley HOD. 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;20:1045–54.
74. Bouchard P, Chabbert-Buffet N, Fauser BCJM. Selective progesterone receptor modulators in reproductive medicine: Pharmacology, clinical efficacy and safety. Fertil Steril 2011;96:1175–89.
75. Wang Y, Jiang X, Wang S. The influence of mifepristone to caspase 3 expression in adenomyosis. Clin Exp Obstet Gynecol 2014;41:154–7.
76. Kettel LM, Murphy AA, Morales AJ, Ulmann A, Baulieu EE, Yen SS. Treatment of endometriosis with the antiprogesterone mifepristone (RU486). Fertil Steril 1996;65:23–8.
77. Chwalisz K, Perez MC, DeManno D, Winkel C, Schubert G, Elger W. Selective Progesterone Receptor Modulator Development and Use in the Treatment of Leiomyomata and Endometriosis. Endocr Rev 2005;26:423–38.
78. Taylor HS, Giudice LC, Lessey BA, Abrao MS, Kotarski J, Archer DF, et al. Treatment of Endometriosis-Associated Pain with Elagolix, an Oral GnRH Antagonist. N Engl J Med 2017;377:28–40.
79. Donnez J, Taylor RN, Taylor HS. Partial suppression of estradiol: a new strategy in endometriosis management? Fertil Steril 2017;107:568–70.
80. Liu X, Nie J, Guo SW. Elevated immunoreactivity against class i histone deacetylases in adenomyosis. Gynecol Obstet Invest 2012;74:50–5.
81. Liu X, Guo SW. A pilot study on the off-label use of valproic acid to treat adenomyosis. Fertil Steril 2008;89:246–50.
82. Liu X, Yuan L, Guo SW. Valproic acid as a therapy for adenomyosis: a comparative case series. Reprod Sci 2010;17:904–12.
83. Liu X, Guo SW. Valproic acid alleviates generalized hyperalgesia in mice with induced adenomyosis. J Obstet Gynaecol Res 2011;37:696–708.
84. Mao X, Wang Y, Carter AV, Zhen X, Guo SW. The Retardation of Myometrial Infiltration, Reduction of Uterine Contractility, and Alleviation of Generalized Hyperalgesia in Mice With Induced Adenomyosis by Levo-Tetrahydropalmatine (/ -THP) and Andrographolide. Reprod Sci 2011;18: 1025–37.
85. Ding D, Liu X, Duan J, Guo SW. Platelets are an unindicted culprit in the development of endometriosis: Clinical and experimental evidence. Hum Reprod 2015;30:812–32.
86. Shen M, Liu X, Zhang H, Guo SW. Transforming growth factor β1 signaling coincides with epithelial-mesenchymal transition and fibroblast-to-myofibroblast transdifferentiation in the development of adenomyosis in mice. Hum Reprod 2016;31:355–69.
87. Zhu B, Chen Y, Shen X, Liu X, Guo SW. Anti-platelet therapy holds promises in treating adenomyosis: experimental evidence [Internet]. Reprod Biol Endocrinol 2016;14:66. Available at: http://rbej.biomedcentral.com/articles/10.1186/s12958-016-0198-1.
88. Benagiano G, Brosens I, Habiba M. Structural and molecular features of the endomyometrium in endometriosis and adenomyosis. Hum Reprod Update 2014;20:386–402.
89. Campo S, Campo V, Benagiano G. Adenomyosis and infertility. Reprod Biomed Online 2012;24:35–46.
90. Wang PH, Yang TS, Lee WL, Chao HT, Chang SP, Yuan CC. Treatment of infertile women with adenomyosis with a conservative microsurgical technique and a gonadotropin-releasing hormone agonist. Fertil Steril 2000;73:1061–2.
91. Hirata JD, Moghissi KS, Ginsburg KA. Pregnancy after medical therapy of adenomyosis with a gonadotropin-releasing hormone agonist. Fertil Steril 1993;59:444–5.
92. Silva PD, Perkins HE, Schauberger CW. Live birth after treatment of severe adenomyosis with a gonadotropin-releasing hormone agonist. Fertil Steril 1994;61:171–2.
93. Huang BS, Seow KM, Tsui KH, Huang CY, Lu YF, Wang PH. Fertility outcome of infertile women with adenomyosis treated with the combination of a conservative microsurgical technique and GnRH agonist: Long-term follow-up in a series of nine patients. Taiwan J Obstet Gynecol 2012;51:212–6.
94. Ozaki T, Takahashi K, Okada M, Kurioka H, Miyazaki K. Live birth after conservative surgery for severe adenomyosis following magnetic resonance imaging and gonadotropin-releasing hormone agonist therapy. Int J Fertil Womens Med 1999;44:260–4.
95. Devlieger R, D'Hooghe T, Timmerman D. Uterine adenomyosis in the infertility clinic. Hum Reprod Update 2003;9:139–47.
96. Lin J, Sun C, Zheng H. Gonadotropin-releasing hormone agonists and laparoscopy in the treatment of adenomyosis with infertility. Chin Med J (Engl) 2000;113:442–5.
97. Mijatovic V, Florijn E, Halim N, Schats R, Hompes P. Adenomyosis has no adverse effects on IVF/ICSI outcomes in women with endometriosis treated with long-term pituitary down-regulation before IVF/ICSI. Eur J Obstet Gynecol Reprod Biol 2010;151:62–5.
98. 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;29:1026–30.
99. Park CW, Choi MH, Yang KM, Song IO. Pregnancy rate in women with adenomyosis undergoing fresh or frozen embryo transfer cycles following gonadotropin-releasing hormone agonist treatment. Clin Exp Reprod Med 2016;43:169–73.
100. Younes G, Tulandi T. Effects of adenomyosis on in vitro fertilization treatment outcomes: a meta-analysis. Fertil Steril 2017;108:483–90.e3.