Review Article

Ulipristal Acetate in Adenomyosis

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Abstract

Adenomyosis is defined as the invasion of the basal endometrium (stroma and glands) into the underlying myometrium. It may lead to abnormal uterine bleeding (AUB), pelvic pain, and infertility. The definitive treatment is hysterectomy. Some conservative measures have been used in patients willing to procreate. Ulipristal acetate is a selective progesterone receptor modulator used to treat AUB caused by leiomyomas. This is a systematic review on the use of ulipristal to treat adenomyosis. Eight eligible articles were retrieved from PubMed, SCOPUS, and Cochrane Library. Only one randomized clinical trial was published until date concerning this matter. It seems that ulipristal acetate induces partial or complete remission of AUB caused by adenomyosis, but the evidence concerning its effect on pelvic pain and the radiologic findings of the disease is conflicting. Nevertheless, given the paucity of data, it is still preliminary to draw any conclusion about the subject.

Keywords: Adenomyosis, infertility, progesterone, receptors, ulipristal acetate, uterine hemorrhage

Introduction

Adenomyosis is defined as the invasion of the basal endometrium (stroma and glands) into the underlying myometrium. The starting point of the disease is the endometrial-subendometrial unit, the *archimetra*, which gradually invades the surrounding layer, the *myometra* and induces hyperplasia of the surrounding myometrium. Thus, it is a hormonal-dependent disease, stimulated by estrogens. These changes in the myometrium ultimately lead to thickening of the uterine walls, which tends to get progressively worse with age, resulting in abnormal uterine bleeding (AUB), pelvic pain, and infertility. Depending on its pattern of distribution, it may be classified as diffuse or focal (also called adenomyoma).[1]

The diagnosis of adenomyosis is highly underestimated given its difficulty. The gold-standard tests to evaluate a patient with suspected adenomyosis are pelvic ultrasound (US) and magnetic resonance imaging (MRI), which may show irregular and asymmetrical thickened uterine walls, scattered cystic areas, and characteristic acoustic shadows. In addition, the endomyometrial junction (usually referred as junction zone) may be thickened – a cut-off of 12 mm is usually considered diagnostic of adenomyosis. Despite the lack of consensus, the presence of endometrial tissue more than 2.5 mm below the junction zone may also be considered additional criteria.[2,3]

The proper management of adenomyosis depends on patient's symptoms. Infertile patients may have dysmorphic uterine cavities and impaired endometrial receptivity resulting in recurrent implantation failure.[4] Metroplasty combined with hormonal treatment based on progestins or GnRH agonists may improve reproductive outcomes.[5]

Nevertheless, the most common symptom is AUB. The definitive treatment of the disease is hysterectomy.

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However, numerous medical treatments have been used to temporarily control heavy bleeding to preserve fertility, avoid surgery or improve patients' condition before hysterectomy. Both combined contraceptive pills and progestins alone (especially dienogest) are effective. However, some patients have contraindication to estrogen therapy, especially in their forties when adenomyosis is more frequent. In addition, symptoms tend to recur after suspending these medications. Intrauterine levonorgestrel-releasing devices are also highly efficient and provide adequate contraception simultaneously, but they are not a solution for patients willing to procreate. Agonists of GnRH, hormonal modulators, such as danazol, or aromatase inhibitors, are also effective and may eventually reduce the extension of the disease. However, they have important side effects and must not be used for long periods. Recently, some alternative therapies have been described such as uterine artery embolization, High-intensity focused ultrasound, endomyometrial ablation, and medical treatment with GnRH antagonists. Preliminary results of some of these treatments are promising, but data are still scarce.[6]

During the last years, selective progesterone receptor modulators (SPRM) have been used to treat AUB caused by leiomyomas. Ulipristal acetate (UPA) is a SPRM used in high doses as emergency contraception. Most recently, UPA has been used to treat AUB due to leiomyomas in daily doses of 5 mg. Most studies report an important reduction in volume and size of leiomyomas after courses of 3 to 6 months of treatment, as well as a high majority of patients experiencing amenorrhea. However, UPA has important side effects, such as weight gain, fatigue and abdominal discomfort.[7] UPA has also a well-known endometrial stimulating effect, which appears to be benign, reversible and of no major concern.[8] Last but not least, some cases of acute hepatic failure and death lead to its temporary withdrawal in some countries.[9]

As a SPRM, hypothesis has been postulated that UPA may eventually be used off-label to treat other steroid-dependent conditions, such as endometriosis and adenomyosis.

Methods

Data sources and study selection

A systematic review of all articles listed in PubMed, SCOPUS, and Cochrane Library was conducted in April 2021 using the query: (adenomyosis) AND (ulipristal OR esmya).

All articles related to UPA in adenomyosis were considered. Articles written in any language other than English, Portuguese, Spanish or French were excluded. No limit of date was set. A thorough review of all references as also performed to recognize potential appropriate studies.

Two reviewers independently performed the selection of the studies. The authors discussed inconsistencies until an agreement was achieved.

Due to the nature of the study, it was neither registered nor did it undergo an ethics committee approval.

Study appraisal

From the initial search, 49 results were retrieved (Pubmed: 10, SCOPUS: 33, Cochrane Library: 6). Duplicates were removed (n = 16). All articles' titles and abstracts were analyzed. Eleven studies related only to leiomyomas were excluded, as well as other 11 related to other matters other than adenomyosis and 1 study due to language issues. References search revealed no additional studies to be included. After full text analysis, 2 articles were excluded because they made no reference to UPA in adenomyosis. In the end, 8 studies were included. [Flowchart 1].

Results

Quality assessment

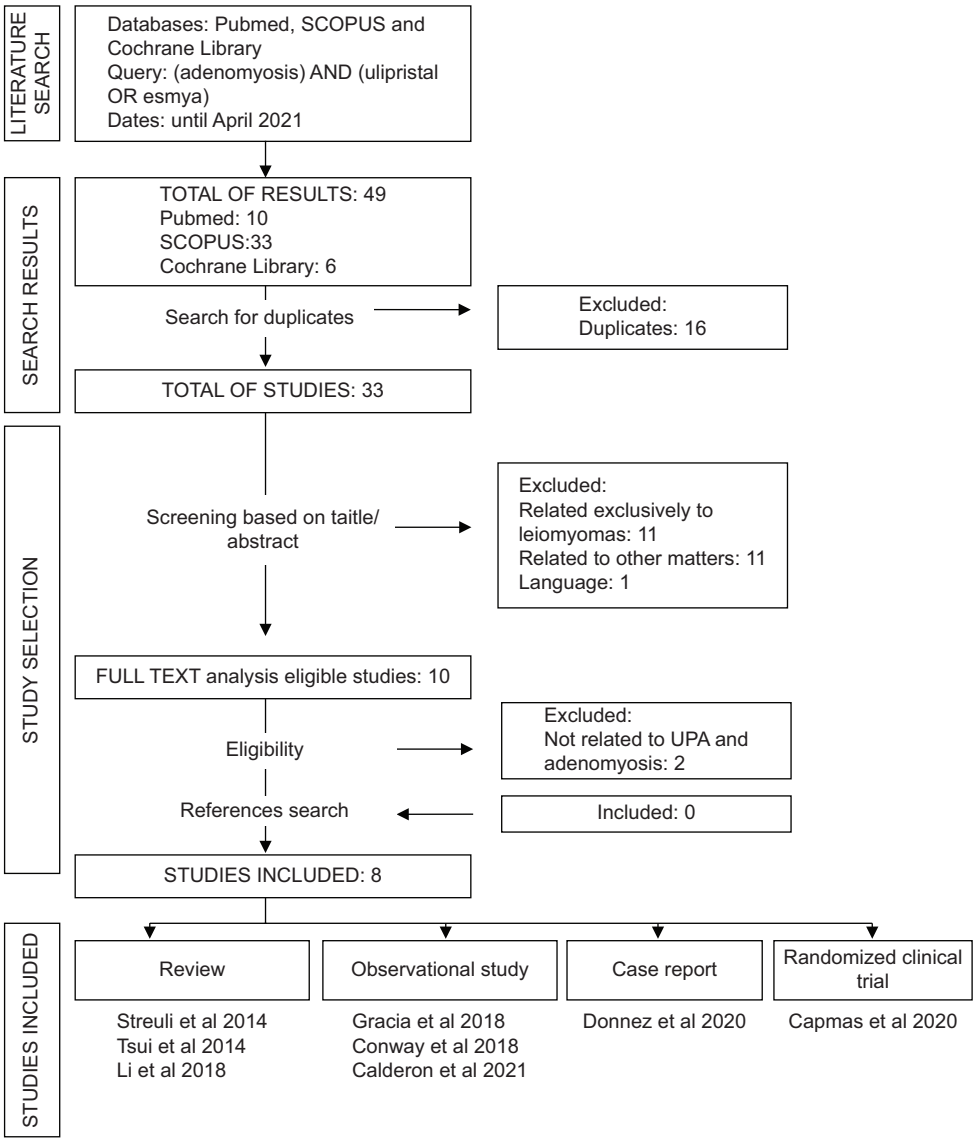
From the 8 articles included, there were 3 reviews, 3 observational studies, 1 case report, and 1 randomized clinical trial (RCT). The 3 reviews were studies about various treatments of adenomyosis, there was no review specifically referring to UPA in adenomyosis.[6,10,11] The 3 observational studies include one cohort study and 2 case series. The cohort study was based on 163 patients and compared 2 groups – patients with leiomyomas alone with patients with concomitant adenomyosis, both groups treated with UPA.[12] In both case, series patients had adenomyosis and were treated with UPA – one including 72 patients and another small cases series of 6 patients.[13,14] The case report was based on a patient with this pathology treated with UPA.[15] There was only 1 RCT, a double-blind phase 2 randomized controlled trial with 48 patients, 36 treated with UPA and 12 treated with placebo.[16]

Mechanisms of action of ulipristal acetate in adenomyosis

Theoretically, UPA could have an effect on adenomyosis due to 2 mechanisms: by inducing amenorrhea and by direct effect on adenomyotic tissue. However, ectopic endometrial tissue is thought to have less progesterone receptors, which may limit the response to UPA.[10] As SPRMs interact directly with the progesterone receptors, allowing the binding of dimers to target gene promoters, leading to a mixed agonist and antagonist activity, their activity will be reduced if there are fewer progesterone receptors.[11] In addition, adenomyosis is not only characterized by the proliferation of epithelial tissue but also inflammation of the surrounding tissue.

Abnormal uterine bleeding

UPA has been used to treat AUB caused by leiomyomas. Most of the experience to date of the use of UPA to treat adenomyosis



Flowchart 1: Flow diagram of study selection (according to PRISMA statement)

is based on patients with leiomyomas who concurrently suffer from this disease, which tends to occur simultaneously.

A retrospective cohort study compared the efficacy of a course of 3 months of daily 5 mg of UPA in patients with leiomyomas and adenomyosis (cases) and patients with leiomyomas alone (controls). UPA was able to induce amenorrhea in 90% of the cases compared to 78% of the controls (P = 0.0017). The proportion of patients with an optimal bleeding control (based on the Pictorial Blood Loss Assessment Chart [PBAC]) was higher in the cases (90.2% vs. 73.8%; P = 0.028).[12]

Another observational study, reporting 6 of erroneous treatment with UPA of supposed leiomyoma when patients, in fact, suffered from adenomyosis, revealed a clear improvement of bleeding (all patients became amenorrheic), despite an important worsening of pelvic pain.[13]

The only RCT published about UPA in adenomyosis compared patients treated with 10 mg of UPA daily during 3 months (30 patients) with placebo (10 patients). This study reported a significant improvement in bleeding after 13 weeks of treatment. The rate of women with a PBAC scores lower than 75 was significantly higher in the UPA group (95.24% vs. 0%, $P < 0.01$). However, there were no differences in neither mid-term evaluations, nor 3 months after suspending treatment (6 months after the starting point). The rate of amenorrhea was also significantly different at 9 weeks (85.7% in the UPA group versus 16.7% in the placebo group, $P < 0.01$) and at 13 weeks (95.2% in the UPA group versus 0% in the placebo group, $P < 0.01$). Again, 3 months after the withdrawing treatment, this difference was not significant (12.5% in the UPA group versus 0% in the placebo group, $P > 0.99$). The authors did not find differences in the rates of anemia between groups.[16]

Pelvic pain

Gracia *et al.* found an improvement in the reported visual analog scale scores in patients treated with UPA.[12] The 2020 RCT found a significant decrease in pain scores 13 weeks after beginning UPA (4.8 in the UPA group vs. 1.7 in the placebo group, $P < 0.01$). However, as for amenorrhea, no significant differences in pain score were observed 3 months after suspending treatment. In addition, the authors did not find differences in quality of life scores between patients treated with UPA and placebo.[16]

On the other hand, previous observational studies report an important worsening of pelvic pain, dysmenorrhea, and bulk symptoms in adenomyotic patients treated with UPA. It is important to notice, however, that this is based on case reports or case series with very small sample sizes.[13,15]

Findings in ultrasound and magnetic resonance imaging

In the retrospective study of Gracia *et al.*, both patients with leiomyomas and adenomyosis or leiomyomas alone had a reduction on uterine volume, with no significant differences between these 2 groups.[12]

The RCT revealed completed resolution of the findings in MRI or US 6 months after starting treatment (3 months after suspending) in 37% of the patients treated with UPA and 0% of the placebo group, but this was not statistically significant ($P = 0.14$). Nevertheless, they found a significant decrease in the depth of adenomyotic invasion in the UPA group (73.3% vs. 0%, $P < 0.01$).[16]

On the other hand, both small reports revealed worsening of pelvic pain and radiologic findings after 3 months of treatment with UPA, not only in the extension of the disease, but also in size and number of lesions. Interestingly, one of these reports shown a good clinical and radiologic recovery of a patient further treated with a GnRH antagonist, linzagolix.[13,15]

In addition, a prospective observational study with 72 patients treated with 5 mg of UPA for 3 months for leiomyomas revealed that 80% of the patients with previous adenomyosis suffered progression of the disease and 26% developed *de novo* adenomyosis. They defined progression of the disease as an increase in thickness of the junction zone of ≥20% and/or increase in the number of intramyometrial cysts.[14]

Discussion

Adenomyosis is a steroid-dependent disease caused by invasion of the myometra by endometrial ectopic tissue, causing reactive inflammation. If so, it seems logical that progestins and modulators of the progesterone receptors may play a beneficial role in these patients, by inducing decidualization and secretory changes and atrophy of the tissue.

It has been postulated that UPA, with its capacity of inducing amenorrhea in patients with AUB caused by leiomyomas, could as well reduce inflammation surrounding the adenomyotic lesions. However, previous studies have demonstrated that ectopic endometrial cells in both adenomyosis and endometriosis have less progesterone receptors activity. In addition, UPA, as a SPRM, may have progesterone agonist and antagonist activity depending on the tissue. Specifically concerning the endometrium, it leads to a benign self-limited hypertrophy. If this is true for the eutopic endometrial tissue, it may also occur in ectopic endometrial cells.

To our knowledge, this is the first review about the use of UPA in adenomyosis. According to the criteria of inclusion and exclusion, 8 studies were included. Three of these studies were generic reviews regarding adenomyosis and its treatment, with quite little information about UPA. The other studies consist of 3 observational studies addressing the evolution of symptoms or radiologic findings of adenomyosis during treatment with UPA, 1 case report, and only 1 RCT.

In respect to AUB, the majority of the studies report an impressive improvement of bleeding in patients treated with UPA for a course of 3 months. It is important to notice that in most cases, patients were treated with UPA due to concomitant leiomyomas, for which UPA has shown to be quite effective. In addition, UPA-induced amenorrhea in most of the patients, independently of the presence of adenomyosis alone, leiomyoma alone, or both problems simultaneously. The RCT reported an important improvement after 3 months of treatment, but after suspending treatment, no differences in AUB were found compared to placebo.

Concerning pelvic pain and bulk symptoms, results are conflicting. Some studies report improvement of these symptoms while others report an evident worsening. However, it is important to notice that patients with leiomyomas were also included, thus, the benefits observed may be attributed to the effect on the leiomyomas and not the adenomyotic tissue. Again, the only RCT reported a temporarily relieve of pain, with no long-term effect after suspending treatment and no effect on overall patients' quality of life.

Regarding the evolution of the disease based on US or MRI, results are also quite conflicting. Most of the studies are based on US or MRI preformed before and after treatment. The only RCT on the subject reports complete resolution of the lesions in 37% of the patients treated with UPA compared to 0 in the placebo group, and 73% of the patients experienced reduction in the depth of invasion. Nevertheless, other 3 studies report opposite results, with important progression of the disease. Two of these studies are based on only 7 patients. The most recent study on the subject was a prospective observational

noncontrolled study with 72 patients, in which 26% developed adenomyosis *de novo* and 80% of the patients with known adenomyosis experienced progression of the disease.

This review is limited by the small number of studies available, their poor quality, and the small sample sizes. In addition, most of the information available addresses other SPRMs, such as mifepristone, due to their better availability and safety profile.

Specific addressing UPA on adenomyosis, only 1 RCT has been published so far, based on a small cohort of patients and giving conflicting results compared to other studies. All the other studies were either observational studies or case reports.

Another important aspect is that the US and MRI criteria of adenomyosis were not consistently defined. In addition, there are no studies addressing the long-term treatment of patients with adenomyosis with UPA.

In the future, it would be interesting to further investigate the effect of UPA in adenomyosis, with well-designed clinical trials, with strict diagnostic criteria and bigger cohorts. Nevertheless, it is important to assure the safety of UPA, especially concerning its potential hepatotoxicity.

In conclusion, based on the current data, it seems that UPA induces partial or complete remission of AUB caused by adenomyosis in patients with or without leiomyomas, but this may be a temporary effect during the course of treatment. Concerning pelvic pain and the effect on US and MRI findings, results are conflicting. Based on the only RCT available, it seems that UPA may play a small beneficial effect, which ends after suspending treatment.

There is scarce research published about the effect of UPA in adenomyosis. Only 1 RCT has been conducted so far. Thus, it seems preliminary to draw any conclusion about the subject.

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Conflicts of interest

There are no conflicts of interest.

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