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ORIGINAL ARTICLE

Ulipristal acetate therapy increases ultrasound features of adenomyosis: a good treatment given in an erroneous diagnosis of uterine fibroids

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ABSTRACT

Ulipristal acetate (UPA) is used for medical treatment of uterine fibroids. The aim of this study was to describe the effects on painful symptoms and the sonographic uterine modifications in patients with adenomyosis erroneously treated with UPA. This is an observational study on six women affected by adenomyosis and treated with three months of UPA (5 mg/24h). The baseline ultrasonography (US) was not performed at out center nor was the diagnosis of fibroids. The patients came to our attention after the treatment with UPA, prescribed by an external physician. During our post-treatment scan we found aspects of adenomyosis, while no fibroids were detected. Symptoms, myometrial and endometrial ultrasound features were evaluated. All patients reported an increase in pelvic pain. At US evaluation intramyometrial cystic areas were found in all six cases (100%). All patients showed an enhancement of adenomyosis features.The intra-myometrial cysts appeared enlarged and the vascularization enhanced when compared to the images of the pretreatment scan. In patients with adenomyosis treated with UPA due to an erroneous diagnosis of uterine fibroids we observed a worsening of the US features of adenomyosis and of the painful symptoms.

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Introduction

Ulipristal acetate (UPA) is a selective progesterone receptor modulator (SPRM) used for medical treatment of uterine fibroids. UPA decreases uterine bleeding and fibroid growth by reducing the formation of new fibroid cells by promoting apoptosis [1–2]. Though UPA may be designed for uterine fibroids, its role in other gynecological conditions, such as endometriosis and adenomyosis, has yet to be established. Clinical trials have shown that SPRM administration can lead to a pattern of benign, nonphysiological, nonproliferative, histological features of the endometrium termed 'Progesteron receptor modulator associated endometrial changes (PAEC)' [3–5]. This effect of SPRMs on the endometrium occurs in 30–70% of patients. Nonetheless studies have demonstrated that it is a benign and reversible condition which usually disappears two months after the end of therapy [2–3]. The effects of SPRMs in the ectopic endometrium have not been determined. Adenomyosis is characterized by the presence of numerous sites of ectopic endometrium within the myometrium [6]. While it is commonly known that fibroids grow under the influence of progesterone it is also known that there is a certain degree of progesterone resistance in patients with adenomyosis [7]. Some experts have proposed that SPRMs might be effective in reducing adenomyosis associated pain by inducing amenorrhea and currently clinical trials are ongoing to explore this particular context [8].

In this study we report the sonographic findings observed during treatment with ulipristal acetate in patients affected by adenomyosis that was misdiagnosed as uterine fibromatosis at transvaginal ultrasound (TVS) and therefore treated with three months of UPA.

Materials and methods

This is an observational study on six premenopausal women who were treated with three months of daily therapy with UPA (5 mg/24h). The treatment was prescribed by an external physician on the basis of a US scan that diagnosed uterine fibroids. The six women included in this study had not received the initial US evaluation at out center and came to our attention during the treatment at two-three months of UPA therapy. A TVS is usually performed before initiating treatment to assess fibroid volume and endometrial status and a follow-up examination is repeated at the end of the three month treatment course with UPA to assess fibroid volume reduction and endometrial appearance. Finally, a TVS scan is performed approximately two months from the end of the treatment, following the first or second spontaneous menstrual period, to evaluate the endometrium. Ideally all the scans should be performed in the same unit, however, this is not always the case.

The follow-up scan, performed in our center by an experienced operator (C.E.), did not show the typical features of myomas at US examination, presenting instead all the sonographic characteristics associated with adenomyosis. During our examination all patients were investigated with ultrasound and the following clinical and ultrasound information were collected:

Clinical examination

A complete medical, surgical and obstetrical history which included the women's age, body mass index (kg/m2), age at menarche, gravidity and delivery mode was recorded. The presence of the following signs and symptoms was noted:

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dysmenorrhea, dyspareunia, functional bowel signs, urinary tract symptoms (dysuria, urgency and hematuria), chronic pelvic pain and abnormal uterine bleeding. Pain severity was evaluated through the visual analog scale (VAS) system, utilizing a 10 cm line with the extreme points 0 and 10 corresponding to 'no pain' and 'maximum pain', respectively. The painful symptoms were assessed during and after the treatment with UPA and the patients were also asked to recall their pain level prior to initiation of treatment and to score it through the VAS.

Ultrasound examination

All sonographic examinations were performed by one experienced examiner (C.E.). The transvaginal ultrasound scan was performed with a GE E6 (GE Healthcare) ultrasound machine, using a wideband 7.5 MHz endocavitary transducer. The scan first involved a conventional 2 D ultrasound assessment of the pelvis to exclude any obvious pathology, followed by visualization of uterus in transverse and longitudinal planes. The myometrium was systematically examined for the presence of any abnormalities. Evaluation of myometrial vascularization by means of power Doppler was always performed. 2 D gray scale and power Doppler vascularization was described according to the MUSA definition. [8]. The 2 D examination was followed by acquisition of 3 D data using the 3 D volume mode. The 3 D volume mode displayed a truncated sector which was adjusted to define the area of interest; the sweep angle was set to 120° to include the entire uterus and a 3 D dataset was then acquired using the high-quality, slow-sweep mode. The resultant multiplanar display of the uterus was examined to confirm its inclusion in its entirety. Also the 3 D volume of the uterus was acquired with and without power Doppler.

Datasets of the uterus from each subject were stored on recordable digital video discs for subsequent analysis. The ultrasound settings, both gray scale and Doppler, were standardized and identical for all subjects.

Diagnosis of adenomyosis was made when any of the recognized features of the disease were observed on the examination. These morphological features have been described previously and there is a wide consensus that they are reliable morphological markers of adenomyosis [9–13]. Briefly the diagnosis of adenomyosis was made when the following features were present: asymmetrical myometrial thickening, myometrial cysts, linear striations, hyperechoic islands or an irregular, infiltrated and thickened endometrial-myometrial junction zone on either two- dimensional or three-dimensional imaging.

Endometrium characteristics where assessed according to the IETA consensus [14]. We evaluated the following aspects: endometrial thickness, endometrial echostructure and the presence of cystic areas. An endometrium that is characterized by an increased thickness and occupied by multiple cystic dilatations during or immediately after treatment with UPA presents the typical aspects of PAEC.

Ethical approval

Ethical approval was sought from and approved by the local research ethics committee who deemed that, as the ultrasound assessments were part of standard clinical practice, full ethical review was not required.

Results

The patient characteristics are listed in Table 1. The symptoms reported by patients during treatment and observed post-treatment with UPA are listed in Table 2. In our series the therapy with UPA significantly controlled uterine bleeding in all patients: at the end of the treatment all women were amenorrheic. In regards to painful symptoms the results of the treatment with UPA were not as satisfying. None of the patients reported an improvement in painful symptoms, in fact most of them reported an increase in pain. Particularly patients that presented with painful symptoms prior to the treatment, such as chronic pelvic pain, dysmenorrhea and dyspareunia, reported a worsening of painful pelvic symptoms during the treatment with UPA. Two patients decided to stop the treatment within the first two months due to an increase in the severity of pain.

Table 3 shows the sonographic findings observed during the follow-up scan post-UPA performed in our unit. Typical aspects of adenomyosis were present in all cases (Figure 1(a)), whereas no typical US signs of uterine fibroids were found. In all six patients we found the presence of intramyometrial cystic areas (100%). When comparing our US images to the initial US examination, that was performed by an external physician, we discovered that the typical aspects of adenomyosis had not been described in the sonographic report or erroneously described as uterine myomas.

Table 1. Patient characteristics.

N. of the case	Age	BMI	Length of treatment with UPA (months)	Amenorrhea
1	50	20.6	3	Yes
2	48	22.0	3	Yes
3	48	24.7	3	Yes
4	46	21.3	3	Yes
5	47	20.7	2	Yes
6	51	21.0	2	Yes
Mean	48.3	21.7	2.6	100%

Table 3. Sonographic findings post UPA treatment.

US findings at follow up scan	*N.* (%)
Intramyometrial cysts	6/6 (100%)
Asymmetrical myometrial walls	4/6 (66%)
Fan shaped shadowing	4/6 (66%)
JZ abnormalities	5/6 (83%)
PAEC	3/6 (50%)
Color score $\geq$3	6/6 (100%)

Table 2. Patient symptoms prior to, during and after UPA treatment.

N. of	Dysmenorrhea (VAS)		Pelvic pain (VAS)			Dyspareunia (VAS)			Bowel symptoms (VAS)		
the case	Prior UPA	Post UPA	Prior UPA	During UPA	Post UPA	Prior UPA	During UPA	Post UPA	Prior to UPA	During UPA	Post UPA
1	6	8	7	9	9	4	5	5	5	6	6
2	7	8	5	5	6	6	7	7	6	7	8
3	5	7	7	8	8	5	5	7	5	5	6
4	6	7	4	4	5	5	6	6	4	6	6
5	7	8	5	7	8	7	9	9	7	8	8
6	7	9	7	8	9	5	8	8	7	8	8
Mean	6.3	7.8	5.8	6.8	7.5	5.3	6.6	7	5.6	6.6	7

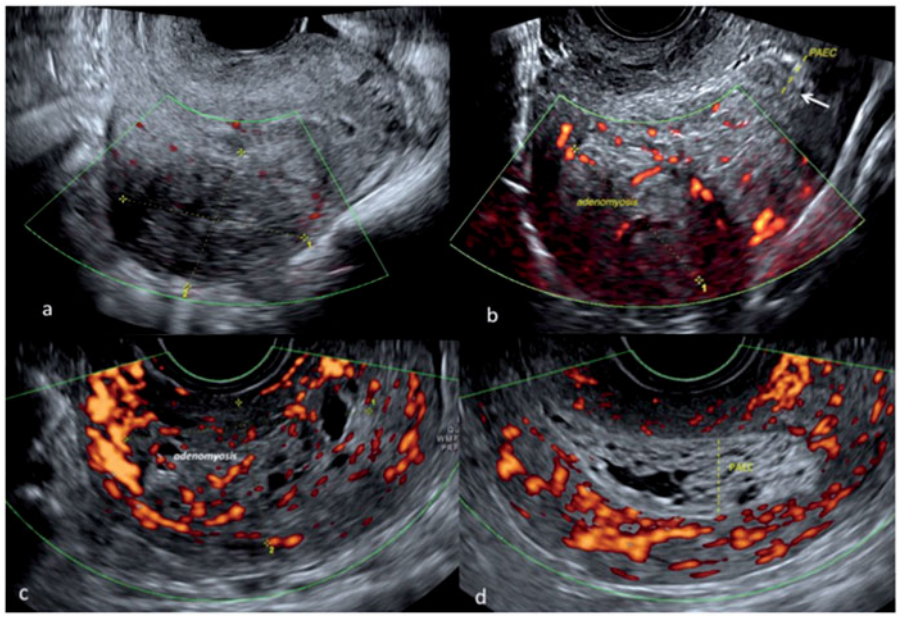

Figure 1. Patient with adenomyosis treated with UPA: (a) Image obtained from the external scan performed prior to the treatment with UPA in which adenomyosis was seen as a fibroid; (b) after 2 months of treatment with UPA TVS images performed in our Department show a thick endometrial layer due to PAEC (white arrows); (c) note the enhanced vascularity of the adenomyotic myometrium and the avascular PAEC (d).

All sonographic features of adenomyosis appeared enhanced at the end of the treatment, especially myometrial wall thickness, vascularity and the intra-myometrial cysts, which were enlarged when compared to the images of the previous scan (Figure 1). The presence of PAEC was observed (Figure 1(d)) in three of the six patients (50%) and these effects on the endometrium were observed in the adenomyotic myometrium as well.

Conclusions

Medical management of gynecological conditions is on the rise mainly for the need to prevent surgery and preserve patient fertility [1]. Although fibroids and adenomyosis may share a common clinical presentation and are both estrogen-dependent diseases, it is very important to keep in mind the very distinct pathogenesis of the two conditions.

Currently medical options are first line treatments for adenomyosis, such as prolonged progestin therapy or LNG IUD [15]. At the present time SPRMs are not recommended for the treatment of adenomyosis since there is no current description of the potential applications of SPRMs other than fibroid treatment and emergency contraception. In his expert opinion review on the safety of UPA Donnez has suggested how SPRMs will probably be effective in the reduction adenomyosis-associated pain by inducing amenorrhea [2]. At the present time there are clinical trials such as the FRA-IIT-UPA exploring the efficiency of UPA on bleeding control and pain management in women with adenomyosis, but no results are available yet [8]. To the best of our knowledge there is no published study that analyses the effects of UPA on patients affected by adenomyosis only. This is the first report to describe the morphological changes at US examination of adenomyotic lesions treated with UPA. We observed a significant improvement of symptoms such as heavy menstrual bleeding (HMB) since amenorrhea was obtained in all patients. Nonetheless, in our series, the UPA-induced amenorrhea did not prove to be effective in controlling pain for patients with adenomyosis. In fact, we observed a worsening of painful symptoms after the treatment with UPA in adenomyosis patients. The augmentation of painful symptoms was reflected by the enhancement of the adenomyotic features that we discovered at US examination when comparing the pretreatment scan presented by the patient to the follow up scan performed in our unit. Our findings show that treatment with UPA increases the entity of adenomyotic uterine lesions, enhancing aspects such as intramyometrial cysts. Further studies are needed to investigate the potential applications of SPRMs in the field of adenomyosis and endometriosis. In our study UPA was prescribed on the basis of a US diagnosis of uterine fibroids which were in fact adenomyotic thickenings of the endometrium misinterpted as fibroids. It seems important to emphasize how the US examination remains an essential tool to correctly identify patients that may actually benefit from UPA. Fibroids and adenomyosis share a very common clinical presentation but usually are characterized by a very distinct sonographic appearance. In some cases substantial diagnostic difficulties may arise because of some overlapping ultrasound features. Nonetheless we believe that adenomyosis is visible on TVS if the operator is aware of the spectrum of findings and their manifestations. All physicians performing TVS should have extensive knowledge of the sonographic appearance of adenomyosis allowing the correct diagnosis and proper treatment for the patient.

Disclosure statement

No potential conflict of interest was reported by the authors.

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