European Journal of Obstetrics & Gynecology and Reproductive Biology 232 (2019) 40–45

Contents lists available at ScienceDirect

European Journal of Obstetrics & Gynecology and Reproductive Biology

journal homepage: www.elsevier.com/locate/ejogrb

Full length article

Sonographic and hysteroscopic endometrial examination in women treated with ulipristal acetate: Exploratory findings at a tertiary referral center

Meritxell Gracia, Roser Nonell, Cristina Ros, Mariona Rius, Lara Quintas, Maria Ángeles Martínez-Zamora, Francisco Carmona*

Department of Gynecology, Institut Clinic of Gynecology, Obstetrics and Neonatology, Hospital Clinic, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Faculty of Medicine-University of Barcelona, Barcelona, Spain

ARTICLE INFO

Article history:
Received 10 August 2018
Received in revised form 31 October 2018
Accepted 5 November 2018

Keywords:
Myomas
Hysteroscopy
Progesterone receptor-associated endometrial changes
Transvaginal ultrasound
Ulipristal acetate

ABSTRACT

Objective: Ulipristal acetate (UPA) is a progesterone receptor modulator (PRM) agent that has shown benefits in women with symptomatic uterine fibroids. However, its effects on the endometrium are complex and not fully understood. We describe exploratory findings on macroscopic observation of the endometrium at transvaginal sonography (TVS) and hysteroscopy. The aim of the study is to characterize endometrial patterns commonly observed after UPA treatment.
Study design: We performed a prospective longitudinal study at a tertiary referral center with 100 women with symptomatic uterine fibroids who received a 12-week treatment with UPA (5 mg/day). Patients underwent TVS before and after the treatment, and also a hysteroscopy examination was performed. Main outcome was to compare sonographic and hysteroscopic findings to histology after UPA treatment.
Results: Twenty one out of 100 (21%) women showed PAEC confirmed by histology after UPA treatment. Ultrasound findings were normal in most women after UPA treatment, but 18/100 (18%) showed an endometrial pattern suggestive of PRM effects (non-uniform, homogeneous endometrium with regular cystic areas). Endometrial thickness ≥16 mm was detected in 6/100 patients (6%), and all of them also presented sonographic PRM pattern. No patient presented malignancy according to histology in this subgroup, and 100% of them had PAEC pattern at histology. Among total patient population showing PAEC at histology, only 33% of these were identified by hysteroscopy, while 57% were identified by TVS with the PRM suggestive pattern. Of note, visibility of endometrium was improved at TVS after UPA.
Conclusion: Identification of increased endometrial thickness together with the categorized endometrial PRM pattern at TVS may be correlated to benign lesions and may not be a cause of concern. This study is exploratory and further research is necessary to support these conclusions. Nevertheless, TVS seems to be feasible to plan adequate follow-up protocols by avoiding unnecessary interventional procedures such as hysteroscopy.

Introduction

Uterine myomas are the most common solid pelvic tumors, with an incidence that ranges between 20%–40% in women of reproductive age [1,2]. Despite being benign, myomas can cause abnormal uterine bleeding (AUB), pain, and subfertility [3]. In the recent years, selective progesterone receptor modulators (PRM) such as ulipristal acetate (UPA) have emerged to treat symptomatic uterine myomas by complementing the surgical procedures.

Standard UPA treatment (one course 5 mg daily up to 12 weeks) rapidly controls bleeding, reduces the size of the myomas, and improves quality of life, along with a good safety profile [4,5]. However, the effects of this drug on the endometrium are complex and not fully understood [6]. Selective PRMs are both progesterone receptor agonists and antagonists, and can have ambivalent effects on different tissues [7]. Indeed, the use of PRMs has been associated with non-physiological histological changes of the endometrium, including progesterone receptor

Abbreviations: IETA, International Endometrial Tumor Analysis; PAEC, Progesterone receptor modulator associated endometrial changes; PRM, Progesterone receptor modulator; TVS, Transvaginal sonography; UPA, Ulipristal acetate.

* Corresponding author at: Hospital Clínic of Barcelona, Department of Gynecology, Villarroel, 170, 08036, Barcelona, Spain.
E-mail address: fcarmona@clinic.ub.es (F. Carmona).

https://doi.org/10.1016/j.ejogrb.2018.11.009
0301-2115/

modulator associated endometrial changes (PAEC) [6,8]. PAECs are defined at histology as inactive and non-vacuolated glandular epithelium with cystically dilated glands; ciliated and eosinophilic metaplasia; low mitotic activity; abnormal vasculature showing ecstatic thin-walled vessels; and aggregates of arteriolar vessels with thickened walls containing smooth muscle cells and "chicken-wire" capillaries [8]. More recently, Bettochi et al. [9] performed a hysteroscopic evaluation of the endometrium from 74 premenopausal women on treatment with UPA to define common hysteroscopic findings after PRM. They observed simultaneous presence of the following aspects: hypotrophic endometrium; secretory endometrium; isolated cysts; floating appearance of the mucosa; and highlighting of the stromal vascular network surrounding the glands, which gives a "chicken-wire" appearance [9].

PAECs have been characterized as benign, non-proliferative, and fully reversible lesions after UPA treatment discontinuation [4,8–11]; however, the heterogeneous and unpredictable nature of PRM effects on the endometrium has been a cause of concern among gynecologists. Moreover, PAECs may alter the sonographic endometrial patterns; namely, endometrial thickening over 16 mm can be observed at transvaginal sonography (TVS) after UPA treatment [4,12]. Despite being reversible after UPA discontinuation [4], this sonographic finding makes clinicians prescribe invasive examinations such as hysteroscopy and biopsy in order to rule out endometrial hyperplasia or cancer. Thus, understanding the effects of PRM on TVS parameters is essential to help clinicians identify benign findings and reduce the number of unnecessary invasive examinations.

TVS is a non-invasive, well-accepted, cost-effective technique that is used in routine practice for the follow-up of patients with myomas. To date, little information is available regarding the effect of PRMs on sonographic endometrial findings. Thus, we designed a preliminary, proof-of-concept study aimed at extending the knowledge of the most common TVS and hysteroscopic endometrial findings after standard UPA treatment.

Material and methods

This prospective longitudinal study was conducted at the Gynecology Department of the Hospital Clinic, a tertiary referral center in Barcelona, Spain. The study was approved by the local Ethical Committee, according to the appropriate regulations and informed consent was obtained from all the patients.

Patients

The study population consisted of 100 premenopausal women recruited consecutively from outpatient consultation within a 12-month period from September 2016 to August 2017. The inclusion criteria were premenopausal status with indication for UPA treatment due to the presence of one or more symptomatic myomas. Namely, women had to present AUB, pelvic pain, and/or pelvic compression. Patients with any endometrial pathology, hormonal treatment within 3 months from initiation of this study, chronic inflammatory pelvic disease, associated adenomyosis, severe medical condition (cardiopulmonary, renal or hepatic problems) or the diagnosis or suspicion of gynecologic cancer were excluded from the study.

Participants were enrolled before UPA treatment and followed prospectively after completion of one standard UPA cycle (Esmya®; Gedeon Richter, Budapest, Hungary). The treatment was administered according to the common practice of the center and the authorized instructions; initiated during the first day of menstruation at 5 mg/day of UPA during 12 weeks [13].

Ultrasonography

Patients included in the study were scanned by TVS within 1 month before starting the treatment (pre-UPA) and after finishing the 12-weeks therapy with UPA (post-UPA), before menstrual bleeding. The ultrasonographic examination was conducted by a Voluson 730 Expert 2D-3D TVS system (GE Healthcare, Milwaukee, Wi, USA), equipped with a type RIC 5–9 H endovaginal probe. All procedures were taken by the same experienced sonographer (CR) at the Gynecology Department of Hospital Clinic.

The following sonographic parameters were evaluated pre- and post-UPA therapy according to the International Endometrial Tumor Analysis (IETA) criteria [14]: endometrial thickness; endometrial echogenicity and pattern (uniform or non-uniform); endometrial midline (linear, non-linear, irregular or not defined); endo-myometrial junction (regular, irregular, interrupted, not defined); colour Doppler assessment was scored within the endometrium (1-no flow; 2-minimal flow; 3-moderate flow; 4-abundant flow). For the intended use of this study, the experienced sonographer described a pattern suggestive for PRM treatment when non-uniform, homogeneous endometrium with regular cystic areas was recorded.

Hysteroscopy and histology

Women in the study subsequently underwent hysteroscopic procedure by a single specialist (RN) in parallel with the second TVS examination. This was conducted with a 5 mm continuous-flow hysteroscope (Bettocchi® Integrated Office Hysteroscope, Karl Storz, Tuttlingen, Germany), without anesthesia. This endoscope has a 2.9 mm rod lens optical system with a high definition camera (Karl Storz). Guided endometrial samples were collected with a 5 F forceps, fixed in formalin, and stained with hematoxylin-eosin for histologic examination. Uterine cavity distension was achieved by an automatic pump (Endomat, Karl Storz). Images were recorded in a digital system (AIDA System, Karl Storz).

In the absence of standardized criteria for the evaluation of endometrial hysteroscopic patterns [15], these were systematically evaluated by our hysteroscopic physicians as per center's standard criteria and according to the features published by Bettochi et al. [9]. Thus, the hysteroscopic features included global endometrial

Table 1
Demographical and clinical characteristics at baseline.

	N = 100
Age (years), mean ± SD	44.01 ± 5.44
Parity, mean ± SD	1.42 ± 1.57
Ethnicity, n (%)	
Caucasian	72 (72)
Other	28 (28)
BMI (kg/m^2), mean ± SD	25.29 ± 5.18
Fibroid type, N (%)	
FIGO 0-2	22 (22)
FIGO 2-5	11 (11)
FIGO 4	56 (56)
FIGO 6	11 (11)
Number of fibroids, median (min-max)	2 (1-8)
Largest fibroid (cc), mean ± SD median (min-max)	171.35 ± 215.24 68.11 (4.19-1012.81)
Symptoms, n (%)	
AUB only	64 (64)
AUB + pelvic pain	32 (32)
Pain	2 (2)
Pelvic pressure	2 (2)
PBAC pre ≥ 100, n (%)	85 (85)
PBAC post <75, n (%)	88 (88)

AUB, abnormal uterine bleeding; BMI, body mass index; FIGO, International Federation of Gynecology and Obstetrics; SD, standard deviation; PBAC, pictorial blood loss assessment chart (≥100, heavy bleeding; <75, optimal bleeding control).

appearance, classified as “proliferative”, “secretory”, “cystic hypotrophy” (atrophic endometrium with marked endometrial gland dilation), or “suggestive of PRM treatment”. In brief, we considered a hysteroscopic “suggestive of PRM treatment” pattern as the simultaneous presence of the following hysteroscopic endometrial aspects, described by Bettochi et al. [9] after UPA treatment: hypotrophic endometrium; secretory endometrium; isolated cysts; floating appearance of the mucosa; and highlighting of the stromal vascular network surrounding the glands, which in terms give a so-called “chicken-wire” appearance.

Histology analysis was conducted by a single blinded pathologist (MA S). PAEC or histological endometrial features for PRM effects were evaluated according to the definition proposed by Mutter et al. [8], i.e., glandular epithelium with inactive and non-vacuolated appearance, and cystically dilated glands, ciliated and eosinophilic metaplasia, low mitotic activity, abnormal vasculature showing ecstatic thin-walled vessels, aggregates of arteriolar vessels with thickened walls containing smooth muscle cells, and “chicken-wire” capillaries.

Statistical analysis

It was performed with the SPSS version 20.0 software (IBM, Armonk, NY, USA). The results of the descriptive analysis of qualitative variables were expressed as frequencies and percentages, and those for the quantitative variables were expressed as medians, or means with standard deviation. Chi-Square and Fisher’s exact tests were used for categorical variables, and the Mann-Whitney test was used for comparison of continuous variables. A p-value <0.05 was considered statistically significant.

Results

Baseline data regarding demographical and clinical characteristics of the women included in the study are described in Table 1. The mean age of patients was 44 years old; and most of them were Caucasian (72%). The number of uterine myomas per patient ranged from 1 to 8, and the volume of the largest myoma (cc) varied from 4.19 to 1012.81 cc, with a mean value of 171.35 ± 215.24. As expected, UPA treatment led to a significant decrease in the fibroid size after the 12-week course (-26.12 ± 93.04).

Clinically, most of the patients presented severe bleeding (PBAC ≥ 100) prior to treatment 85/100 [85%] and after completion of the first UPA course, significantly more women showed optimal bleeding control 88/100 (PBAC < 75). 81% of women, presented amenorrhea (35 consecutive days, as it was defined in the PEARL studies).

TVS findings are presented in Table 2. The mean endometrial thickness did not increase significantly after UPA treatment compared to baseline (6.28 ± 4.15 pre-UPA vs. 7.78 ± 5.73 post-UPA; p = NS); however, 6% (6/100) of women showed abnormally thickened endometrium (≥16 mm) after UPA treatment (p = 0.04).

After UPA therapy, 75% of patients (75/100) had a sonographic uniform endometrial pattern based on IETA criteria [14], while 18% (18/100) presented a non-uniform endometrial pattern not found at baseline: a non-uniform, homogeneous endometrium with regular cystic areas (Fig. 1A and Table 2, p < 0.05). We defined the presence of these sonographic aspects as a sonographic pattern suggestive of PRM effect. Interestingly, all patients with endometrial thickness ≥16 mm showed a sonographic pattern suggestive of PRM effect (Suppl. Table 1).

To note, the measurability of all IETA parameters at TVS was improved after UPA treatment, reaching statistical significance in endometrial midline visualization (p < 0.05) but no significant changes were observed in the endo-myometrial junction or colour Doppler (Table 2).

Endometrial patterns evaluated by hysteroscopy and histologic findings are shown in Figs. 1B and 2 , and Table 3. We next compared the sonographic and hysteroscopic findings with the histology results: overall, 57.14% (12/21) of patients with PAEC at histology presented a suggestive pattern of PRM effect at TVS. In contrast, 33.33% (7/21) of patients with PAEC presented a

Table 2
TVS findings before and after UPA treatment (based on IETA criteria [14]).

	Pre-UPA	Post-UPA	
	n = 100	n = 100	p-value
Endometrial thickness (mm), mean ± SD	6.28 ± 4.15	7.78 ± 5.73	NS
<16 mm, n (%)	89 (89)	84 (84)	<0.05
≥16 mm, n (%)	0	6 (6)	
Not measurable, n (%)	11 (11)	10 (10)	
Endometrial echogenicity and pattern, n (%)			<0.05
Uniform			
Hyper-echogenic	39 (39)	44 (44)	
Iso-echogenic	28 (28)	18 (18)	
3-layer pattern	22 (22)	13 (13)	
Hypo-echogenic	0 (0)	0 (0)	
Suggestive of PRM effect			
(Non-uniform, homogeneous, with regular cystic areas)	0 (0)	18 (18)	
Not measurable, n (%)	11 (11)	7 (7)	
Endometrial midline, n (%)			<0.05
Linear	65 (65)	81 (81)	
Non-linear	0 (0)	0 (0)	
Irregular	0 (0)	0 (0)	
Not defined	35 (35)	19 (19)	
Endo-myometrial junction, n (%)			NS
Interrupted	51(51)	45 (45)	
Regular	36 (36)	40 (40)	
Irregular	0 (0)	0 (0)	
Not defined	13 (13)	15 (15)	
Colour Doppler assessment (score), n (%)			NS
1 (no flow)	13 (13)	7 (7)	
2 (minimal flow)	87 (87)	93 (93)	
3 (moderate flow)	0 (0)	0 (0)	
4 (abundant flow)	0 (0)	0 (0)	

NS, not significant; PRM, progesterone receptor modulators; TVS, transvaginal ultrasound; UPA, ulipristal acetate.

suggestive pattern of PRM effect at hysteroscopy (p = 0.1) (Table 4 and Supp. Table 2) When the subset of patients with endometrial thickness ≥16 mm was evaluated, we found that 100% of those patients had PAEC at histology. As mentioned above, all of them also presented a suggestive pattern of PRM effect at TVS. In contrast, 33.33% (2/6) of patients with endometrial thickness ≥16 mm and PAEC presented a concomitant hysteroscopic pattern suggestive of PRM effect (Table 4 and Supp. Table 2).

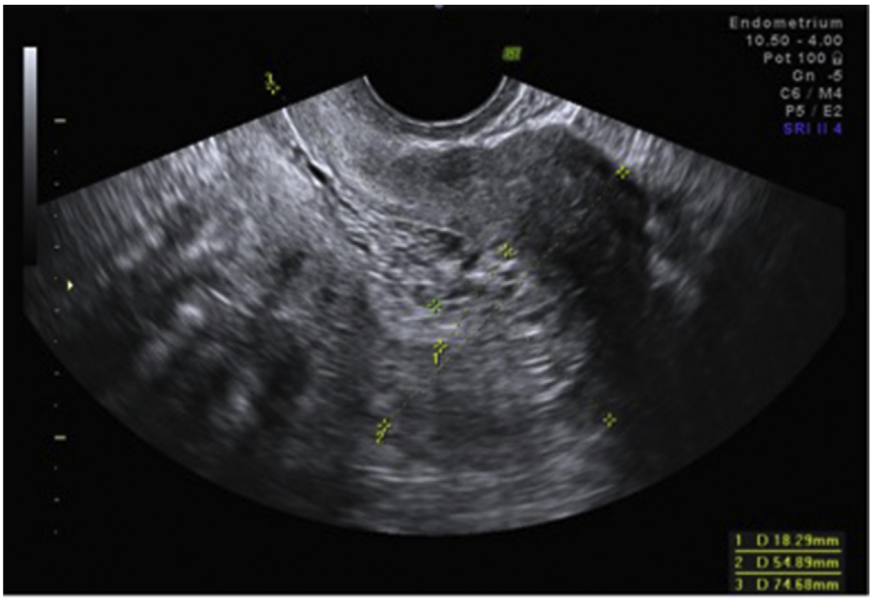
No cases of hyperplasia or malignancy were found.

Comment

To our knowledge, this is the first study describing a specific endometrial evaluation by TVS before and after treatment with UPA. This exploratory study included 100 patients who in addition to a sonographic examination also underwent hysteroscopy and histology to compare and confirm, respectively, the endometrial changes after UPA observed by TVS.

Currently, PAEC is well-defined by histologic parameters [8], but the impact on the endometrial signs at TVS or hysteroscopy and the subsidiary clinical effects are unclear [9]. The incidence of PRM effects on the endometrium ranged from 10 to 25% [5,9], although several authors have reported up to 62% of patients with PRM effects when measured during UPA treatment [4,16]. In our study, 21% of women presented PAEC at histology. Thus, our data are in line with the abovementioned numbers (10–25%). In a more recent publication [9], hysteroscopic patterns related to UPA treatment were present on 44.6% of the sample, but they also counted secretory endometrial patterns by hysteroscopy. From our point of view, this is not a sole characteristic of the PRM changes in the endometrium.

a



b

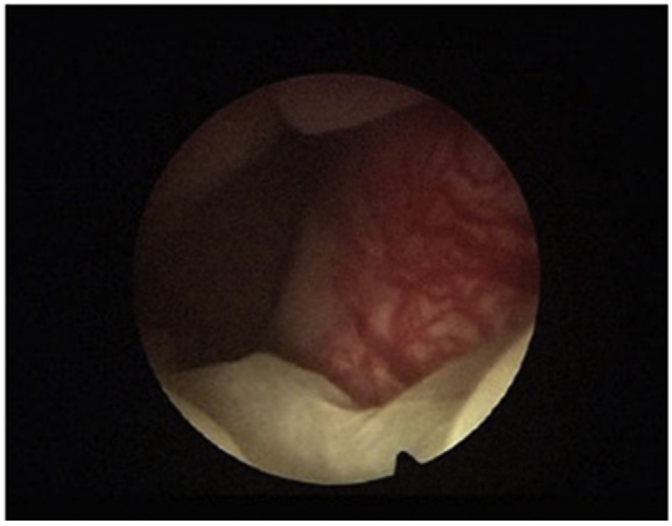


Fig. 1. Images of sonographic and hysteroscopic patterns suggestive of PRM effect in the endometrium. **A.** Transvaginal ultrasound findings suggestive of PRM effect. Endometrial thickness of 18.2 mm described as a pseudocystic non-homogeneous pattern according to the IETA criteria. [14] **B.** Hysteroscopy shows areas with cystic atrophy, floating areas, and a "chicken-wire" vessel pattern according to the hysteroscopic pattern suggestive of PRM effect described by Bettochi et al. [9].

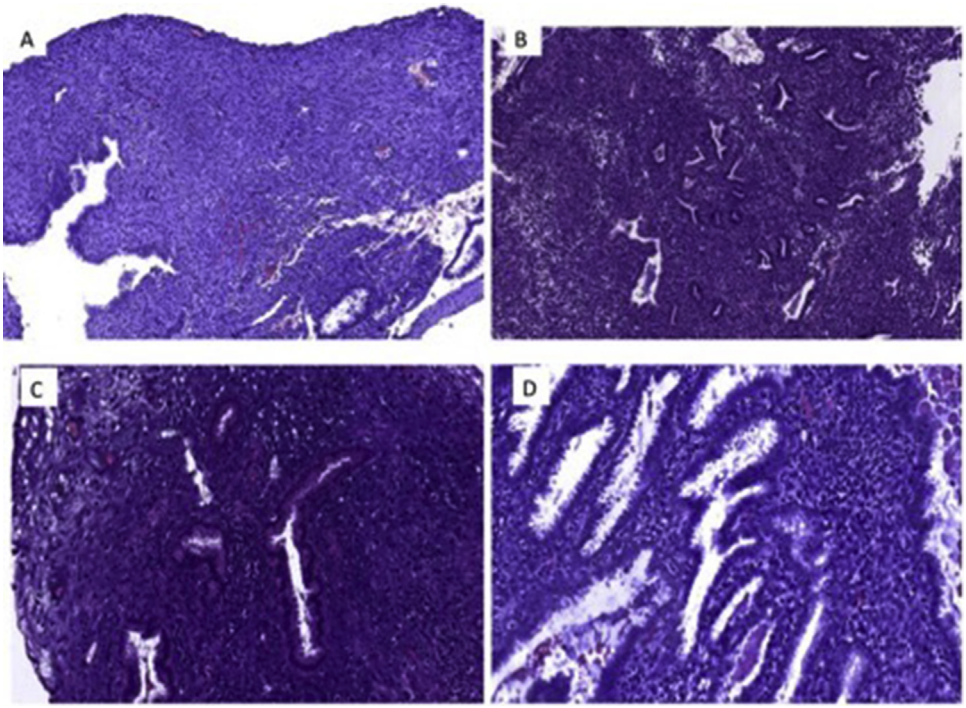


Fig. 2. Histology patterns after UPA treatment. Images show inactive epithelial cells and glands with cystic dilatation (A); multicystic endometrium (B); dilated glands and vacuoles (C); punctuated glands by apoptotic bodies, low mitotic activity (D).

After UPA treatment, endometrial thickness increases in some patients; thus categorizing ultrasound or hysteroscopic endometrial patterns typical of UPA treatment is essential [9,17] We detected abnormal endometrial thickening (≥16 mm) by TVS examination in 6% of the patients, in line with previous investigations (7.4%) [12]. Endometrial thickening was associated to PAEC in our series at histology and no malignancy or cancer was diagnosed in any of the women. In agreement with our data, Bettochi et al. [9] also concluded that increased endometrial thickness at TVS in UPA patients may be correlated to benign lesions induced by UPA, consisting of hypotrophy, isolated as well as confluent cysts, and vascular wall thickening in hysteroscopy. Thus, we suggest that the combination of endometrial thickening plus a pattern suggestive of PRM at TVS could not be a cause of concern, but a result of benign changes induced by UPA. Moreover, measurability of endometrial parameters increased after UPA treatment: visibility of the endometrial midline was significantly improved after UPA, probably due to its activity by reducing the size of the fibroids and uterus. However, treatment with UPA did not affect any other endometrial parameters, as no significant changes were observed in endo-myometrial junction or colour Doppler at TVS.

Table 3
Hysteroscopic and histologic patterns after UPA treatment.

	Post-UPA (n = 100)
Hysteroscopic pattern, n (%)	
Proliferative	41 (41)
Secretory	39 (39)
Cystic hypotrophic	12 (12)
Suggestive of PRM treatment	8 (8)
Histologic pattern, n (%)	
Proliferative	40 (40)
Early secretory	27 (27)
PAEC	21 (21)
Hypoplasic	8 (8)
Mid secretory	4 (4)

PAEC, progesterone receptor modulator associated endometrial changes; PRM, progesterone receptor modulators.

Table 4
Sonographic and hysteroscopic findings in patients with PAEC at histology.

Patients with PAEC at histology (n = 21)	p = 0.1
Sonographic endometrial PRM pattern, n (%)	12 (57.14%)
Hysteroscopic endometrial PRM pattern, n (%)	7 (33.33%)
Patients with PAEC at histology and endometrial thickness ≥16 mm (n = 6)	p = 0.03
Sonographic, n (%)	6 (100%)
Hysteroscopic, n (%)	2 (33.33%)

PAEC, progesterone receptor modulator associated endometrial changes; PRM, progesterone receptor modulators.

In this study we selected the parameters available in the literature [8,9,14], and used our experience as a tertiary referral center to define a sonographic endometrial pattern suggestive of PRM effect. This pattern presents with a non-uniform, homogeneous aspect and regular cystic areas (see Fig. 1A for an example). However, due to the limitation on standardized descriptors and the paucity of previous studies, it is difficult to accurately calibrate our results on the sonographic and hysteroscopic endometrial patterns after UPA treatment. Probably, further randomized studies will be more evident scientifically.

Despite the low sample size and exploratory nature of the study, our results show that: i) A sonographic endometrial pattern suggestive of PRM effects consisting of a non-uniform, homogeneous endometrium with regular cystic areas can be detected after UPA treatment; ii) This sonographic pattern suggestive of PRM effect has a significant correlation with histological PAEC when the endometrial thickness ≥16 mm is observed; and iii) Despite concerns about possible difficulties in parameter visualization at TVS, in our series this has not been a major issue, since visualization improved after UPA treatment.

TVS is used as routine practice in follow-up of women with myomas, and is a cost-effective, non-invasive, painless diagnostic

procedure with good sensitivity and specificity for the detection of intrauterine pathologies leading to AUB [17]. Our results suggest that TVS could be of use for endometrial observation during PRM treatment. Adequately powered prospective studies should be performed to confirm whether TVS could preclude the need for repeated hysteroscopies to assess endometrial changes caused by the use of PRM treatment in the future.

Conflicts of interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ejogrb.2018.11.009.

References

[1] Ryan G.L., Syrop CH, Van Voorhis BJ. Role, epidemiology, and natural history of benign uterine mass lesions. Clin Obstet Gynecol 2005;48:312–24.
[2] Wallach EE, Vlahos NF. Uterine myomas: An overview of development, clinical features, and management. Obstet Gynecol 2004;104:393–406.
[3] Parker WH. Etiology, symptomatology, and diagnosis of uterine myomas. Fertil Steril 2007;87:725–36.
[4] Donnez J, Tatarchuk TF, Bouchard P, Puscasiu L, Zakharenko NF, Ivanova T, et al. Ulipristal acetate versus placebo for fibroid treatment before surgery. N Engl J Med 2012;366:409–20. https://doi.org/10.1056/NEJMoa1103182.
[5] Donnez J, Tomaszewski J, Vázquez F, Bouchard P, Lemieszczuck B, Baro F, et al. Ulipristal acetate versus leuprolide acetate for uterine fibroids. N Engl J Med 2012;366:421–32.
[6] Kannan A, Bhurke A, Sitruk-Ware R, Lalitkumar PG, Gemzell-Danielsson K, Williams ARW, et al. Characterization of molecular changes in endometrium associated with chronic use of progesterone receptor modulators: Ulipristal acetate versus mifepristone. Reprod Sci 2018;25:320–8.
[7] Tafi E, Scala C, Leone Roberti Maggiore U, Bizzarri N, Candiani M, Venturini PL, et al. Drug safety evaluation of ulipristal acetate in the treatment of uterine fibroids. Expert Opin Drug Saf 2015;14:965–77.
[8] Mutter GL, Bergeron C, Deligdisch L, Ferenczy A, Glant M, Merino M, et al. The spectrum of endometrial pathology induced by progesterone receptor modulators. Mod Pathol 2008;21:591–8.
[9] Bettocchi S, Baranowski WE, Doniec J, Ceci O, Resta L, Fascilla FD, et al. Hysteroscopic patterns in women on treatment with ulipristal acetate 5 mg/day: A preliminary study. J Minim Invasive Gynecol 2016;23:664–9.
[10] Fiscella J, Bonfiglio T, Winters P, Eisinger SH, Fiscella K. Distinguishing features of endometrial pathology after exposure to the progesterone receptor modulator mifepristone. Hum Pathol 2011;42:947–53.
[11] Ioffe OB, Zaino RJ, Mutter GL. Endometrial changes from short-term therapy with CDB-4124, a selective progesterone receptor modulator. Mod Pathol 2009;22:450–9.
[12] Donnez J, Donnez O, Matule D, Ahrendt HJ, Hudecek R, Zatik J, et al. Long-term medical management of uterine fibroids with ulipristal acetate. Fertil Steril 2016;105: 165–73e4.
[13] Esmya. Summary of product characteristics. Available at:. http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002041/human_med_001542.jsp&mid=WC0b01ac058001d124.
[14] Leone FP, Timmerman D, Bourne T, Valentin L, Epstein E, Goldstein SR, et al. Terms, definitions and measurements to describe the sonographic features of the endometrium and intrauterine lesions: A consensus opinion from the International Endometrial Tumor Analysis (IETA) group. Ultrasound Obstet Gynecol 2010;35:103–12.
[15] Dotto JE, Lema B, Dotto JE, Hamou J. Classification of microhysteroscopic images and their correlation with histologic diagnoses. J Am Assoc Gynecol Laparosc 2003;10:233–46.
[16] De Milliano I, Van Hattum D, Ket JCF, Huirne JAF, Hehenkamp WJK. Endometrial changes during ulipristal acetate use: A systematic review. Eur J Obstet Gynecol Reprod Biol 2017;214:56–64.
[17] Williams ARW, Bergeron C, Barlow DH, Ferenczy A. Endometrial morphology after treatment of uterine fibroids with the selective progesterone receptor modulator, ulipristal acetate. Int J Gynecol Pathol 2012;31:556–69.