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# Hysteroscopic Patterns in Women on Treatment With Ulipristal Acetate 5 mg/day: A Preliminary Study

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**ABSTRACT** **Study Objective:** To describe the hysteroscopic findings in women on treatment with ulipristal acetate (UPA) and to define the most common hysteroscopic patterns related to the treatment and compare them with the histologic findings.

**Design:** Preliminary study.

**Setting:** OB-GYN and Gynecology Oncology Clinic, Military Medical Institute, Ministry of Defense, Warsaw, Poland, and Obstetrics and Gynecology Department, University of Bari, Italy.

**Patients:** Seventy-four premenopausal patients complaining of abnormal uterine bleeding due to uterine myomas and on treatment with UPA 5 mg/day for at least 30 days.

**Interventions:** Women received transvaginal sonography (TVS) and then office hysteroscopy and visually guided endometrial biopsies. Video hysteroscopies were recorded in digital format. Pictures were evaluated by 2 authors off-line and compared with histologic results.

**Measurements and Main Results:** Hysteroscopic aspects and classification of progesterone receptor modulator–associated endometrial changes were measured. The most common hysteroscopic finding was the combination of a flat subtle epithelium with small glandular openings; large isolated or confluent cysts in the stroma, giving the surface a floating aspect at fluid distention; and well-evident subendometrial vascular network with a "chicken-wire" vascular pattern (44.6%). This finding accounted for 82% of cases with endometrial thickness $>$ 10 mm at TVS. Histology confirmed a combination of epithelial secretory (vacuoles) and hypotrophic effects (small and dilated glands), whereas at stromal level the combination of cysts, dense stroma, and vascular wall thickening was found. At 3 months follow-up echographic, hysteroscopic, and histologic endometrial patterns were normal in all patients.

**Conclusions:** In most women on UPA and with thickened endometrium at TVS, the hysteroscopy showed benign and characteristics aspects related to the ambivalent effects of UPA on progesterone receptor. These alterations took place just after 1 month of treatment but disappeared within 3 months of stopping treatment. Journal of Minimally Invasive Gynecology (2016) 23, 664–669 © 2016 AAGL. All rights reserved.

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Progesterone receptor modulators (PRMs) are synthetic compounds that interact with the progesterone receptor (PR) to inhibit or stimulate the downstream hormonal response [1,2]. Ulipristal acetate (UPA) is a derivative of 19-norprogesterone, acting as potent orally active PRM.

Progesterone may stimulate myoma growth, and data in the literature demonstrated that UPA is effective in reducing myoma volume [3,4]. Accordingly, in the United States and Europe the use of UPA was approved for the preoperative treatment of uterine myomas mainly on the basis of 2 main studies, one showing the superiority of UPA versus placebo and the other the noninferiority versus

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gonadotropin-releasing hormone agonist to reduce both excessive uterine bleeding and myoma volume before surgery [3,4]. More recently, the effectiveness of repeated treatment with UPA was also demonstrated [5].

Assessment of the effects of PRMs on the endometrium is of primary interest in ensuring long-term safety of these compounds. Administration of PRMs in premenopausal women who are actively producing estrogens is of some concern because protracted estrogenic stimulation of the endometrium has been associated with a dose- and duration-dependent 2- to 10-fold increased risk for endometrial cancer [6]. In fact, under physiologic conditions it is the intermittent production of progesterone during the luteal phase of the menstrual cycle that opposes the mitogenic effects of estrogens.

Notably, because the pharmacologic effects of PRMs on PR are not homogeneous and not only restricted to the PR itself, the endometrial changes related to PRMs are molecule-dependent and unpredictable based on the prevalence of agonistic or antagonistic effects. The result is that the endometrial patterns induced by PRMs are different from those commonly encountered in contemporary clinical practice. In 2006, during a workshop held at the Centre for Population Research at the National Institute of Child Health and Human Development, Bethesda, Maryland, the PRM effects on the endometrium were presented and discussed. The patterns were histologically categorized as "inactive," "proliferative," or "secretory," with a further subdivision of glandular architecture as "normal" or "disordered." The term "disordered glandular architecture" was used to describe glands in which there was tortuosity of the normal gland structure. All different aspects of the endometrium as observed under the action of PRMs have been grouped under the name of PRM-associated endometrial changes (PAECs) [6].

From a clinical point of view, PAECs may alter the ultrasonographic endometrial patterns, and this may indicate invasive examinations like hysteroscopy. However, PAECs are unknown entities also for the endoscopist because they have never been described and classified before. Therefore, the aim of this study was to describe the hysteroscopic findings in women on treatment with UPA and to define the most common hysteroscopic patterns related to the treatment and compare them with the histologic findings.

## Methods

The study was performed at the OB-GYN and Gynecology Oncology Clinic, Military Medical Institute in Warsaw, Poland and at the Obstetrics and Gynecology Department University of Bari, Italy. This pilot study was based on all 74 women who were under treatment at our institutes with 5 mg UPA a day for at least 30 days. All patients were premenopausal with abnormal uterine bleeding due to uterine myomas. The study protocol was approved by the Local Ethical Committee, and women were included in this study after signing an informed consent form. All the patients agreed to the study.

All women underwent transvaginal ultrasound evaluation to assess endometrial thickness and endometrial echographic characteristics based on International Endometrial Tumor Analysis (IETA) criteria [7]. Picture images were recorded in digital form. Women subsequently underwent office hysteroscopy associated with visually guided endometrial biopsies. Hysteroscopy is considered as a tool for the gynecologists in the workup of uterine myomas [8].

Patients were awake during these procedures performed in office setting with no anesthesia. In particular, hysteroscopies were performed using an Office Hysteroscope (B.I.O.H.; Karl Storz, Tuttlingen, Germany), a 300-W xenon light source (Karl Storz), together with a high-definition camera (Image1; Karl Storz). Images were recorded in digital format (AIDA System; Karl Storz). Distention of the uterine cavity was ensured by a constant pressure of 45 mmHg controlled by an automatic pump (E.A.S.I. Endomat: Karl Storz). Visually guided endometrial sampling was performed using 5F crocodile forceps. Samples were then fixed in formalin and hematoxylin-eosine stained. Histologic examinations were performed by a single author (LR). According to the literature [6], attention was focused on the following histologic findings: glandular atrophy, gland's dilatation, secretory aspect with vacuoles, apoptosis, vessels thickening, and hyaline thrombi.

Examination of the hysteroscopic images were performed offline by 2 authors (SB and EC) who reviewed all images stored with the aim of agreeing on the definition of some endometrial aspects related to UPA treatment. For the description of hysteroscopic aspects, conventional criteria reported in the literature were used [9]. The findings at transvaginal sonography (TVS), hysteroscopy, and histology were compared. Three months after treatment in women who did not undergo hysterectomy, TVS, hysteroscopy and, endometrial biopsy were repeated.

For statistical evaluation values were compared with Student's *t* test. Correlation between different findings at hysterscopy and endometrial thickness at TVS was calculated by using Epistat statistical software (http://archives.math.utk.edu/software/msdos/statistics/epistat/). A p value of .05 was considered as limit of significance.

## Results

Main clinical data regarding women enrolled in the study are reported in Table 1. All women per protocol were complaining of abnormal uterine bleeding due to uterine myomas and were treated with UPA for at least 30 days. Patient age ranged from 31 to 42 years and the duration of treatment from 30 to 50 days. The size of the biggest myoma was between 35 and 60 mm, and the number of myomas per patient ranged from 1 to 4. Findings at TVS, hysteroscopy, and histology are displayed in Table 2.