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Original Article

Endometrial Changes in Surgical Specimens of Perimenopausal Patients Treated With Ulipristal Acetate for Uterine Leiomyomas

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Summary: Ulipristal acetate (UPA) is used to treat leiomyomas, and its effect on the endometrium has been studied in biopsy material. Reversible histologic modifications were found, named progesterone receptor modulators–associated endometrial changes (PAEC). However, hysterectomies from patients treated with UPA have not been analyzed. For the first time, we examined surgical specimens from 100 leiomyoma-treated patients for UPA-related endometrial changes. We analyzed the distribution of lesions, involution after treatment, and the relationship between type and extent of lesions and dosage. Clinically, 72 patients were treated with 1 cycle of UPA; 23 patients with 2 cycles, and 5 with 3 cycles. A total of 66 patients underwent surgery in the first 4 wk after treatment, 24 were operated between 5 and 12 wk after discontinuation of UPA, and 10 after more than 12 wk after the last cycle, up to a maximum of 32 wk. Histologically normal endometria were found in 41 cases and PAEC in 59 cases. PAEC consisted of irregular, cystic glands showing a flattened secretory-like epithelium with vacuolation, coexisting mitoses and apoptosis, and were found focally within cyclic endometria in 51 cases. Only in 8 cases did diffuse PAEC involve the whole endometrium, transforming it into a thick spongy cushion. PAEC also occurred in adenomyosis. There was no relationship between dosage and type and extent of lesions. Diffuse PAEC, which usually presents differential diagnoses with hyperplasia, occurred in only 8 cases, being only present during the first 4 wk after discontinuation of treatment and was independent of the number of cycles administered. **Key Words:** Endometrium—Ulipristal acetate—Histologic changes—Hyperplasia—Adenomyosis—Leiomyoma treatment.

Selective progesterone receptor modulators (SPRMs) interact with progesterone receptors either by inhibiting or stimulating cellular responses. Ulipristal acetate (UPA) is an SPRM mainly used clinically in the treatment of leiomyomas (1–4), in which it achieves both a marked reduction in size and an improvement in concomitant anemia symptoms. UPA is also used as an emergency contraceptive (5,6) and in the treatment of both endometriosis (7) and profuse uterine bleeding.

The effects of SPRMs on the endometrium have been histopathologically described as unusual but reversible, epithelial, stromal, and vascular modifications named as progesterone receptor modulators–associated endometrial changes (PAEC). Because of their relative histologic complexity, they may be confused with hyperplasia and premalignant complex endometrial lesions and polyps. All previous studies dealing with PAEC have been performed on follow-up endometrial

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biopsy material during and after treatment. However, a study of their general architecture, histology, and macroscopic appearance in surgical resection specimens has not been conducted previously.

In the present paper we analyze, for the first time, UPA-related posttreatment endometrial changes in the surgical specimens of one hundred consecutive patients. We attempt to determine the distribution of lesions, patterns of involution after treatment, and the relationship between type and extent of lesions and dosage.

MATERIALS AND METHODS

Clinical Data

We studied 122 consecutive, routine surgical specimens of all cases of patients treated with UPA for uterine leiomyomas, starting from the onset of UPA treatment in 2 centers from January 2014 to December 2016. Fifty-nine were total abdominal hysterectomies, 45 subtotal hysterectomies, and 18 hysteroscopically resected submucous leiomyomas. Twenty-two cases were not included in the final study because of an insufficient amount of interpretable endometrium, autolysis, or thermal resection artifact in the endometria overlying leiomyomas.

In the final 100 selected cases, the patients' ages ranged from 29 to 54 yr, with an average age of 45, and all were premenopausal. A total of 32 patients were included in the study in the year 2014, 25 in 2015, and 43 in 2016. An UPA cycle consisted in the daily oral administration of 5 mg of UPA for 3 mo. Seventy-two patients had been treated with only 1 cycle; 23 patients were treated with 2 cycles separated by the length of 2 menstrual cycles. Only 5 patients had received 3 cycles.

A total of 66 patients underwent surgery in the first 4 wk after UPA treatment, once a reduction in the size of the leiomyoma was achieved. Twenty-four patients were operated between 5 and 12 wk after discontinuation of UPA treatment and 10 after more than 12 wk after the last UPA cycle (maximum 32 wk).

Pathology

Adequate endometrium-containing blocks ranged from 3 to 8 per case with an average of 4. Hematoxylin and eosin slides were analyzed independently by 4 pathologists (F.F.N., C.B., V.C.L., and N.C.-V.). Histopathologic endometrial features were evaluated using parameters outlined in a previous paper, which defined the histology of PAEC (4). They included cyclic status, presence, extent and distribution of glandular cysts with nonphysiological epithelial changes, stromal modifications such as edema, and vascular changes such as chicken-wire capillaries seen on hysteroscopy, as well as dilated and thick-walled vessels. The presence of tubal metaplasia, polyps, adenocarcinoma, and hyperplasia with or without atypia was noted.

Because of the relatively small size of this study, statistical analysis was not performed.

RESULTS

We examined and evaluated 2 histopathologic groups: (a) cases presenting only with normal cyclic endometria and (b) PAEC. Among the latter, focal and diffuse changes were investigated in relationship with UPA dosage and the time elapsed after discontinuation of treatment and subsequent surgery. The results correlating the presence of histology, UPA dosage, and time elapsed after cessation of treatment are summarized in Table 1. There were no cases of adenocarcinoma, hyperplasia, or atypical hyperplasia; unremarkable endometrial polyps were found in 8 cases.

Normal Endometria

Histology

Forty-one cases showed cyclic endometria without any noteworthy histologic changes, lacking glandular cysts or epithelial abnormalities. Of these, 22 were of secretory type, 11 proliferative, and 8 atrophic.

Relationship Between Cases Showing a Normal Endometrial Histology, UPA Dosage, and Time Elapsed After Discontinuation of Treatment

Thirty patients had received 1 cycle; 10, two cycles and only 1, three cycles. Normal endometria were

TABLE 1. *Correlation Between Histologic Findings, Ulipristal Acetate Dosage, and Time Elapsed After Cessation of Treatment*

Endometrium	Time After Surgery (wk)			Total
Normal	<4	5–12	>12	
1 cycle	19	7	4	30
2 cycles	7	2	1	10
3 cycles	1	0	0	1
Focal PAEC	<4	5–12	>12	
1 cycle	21	12	5	38
2 cycles	8	3	0	11
3 cycles	2	0	0	2
Diffuse PAEC	<4	5–12	>12	
1 cycle	4	0	0	4
2 cycles	2	0	0	2
3 cycles	2	0	0	2
Total cases	66	24	10	100

PEAC indicates progesterone receptor modulators-associated endometrial changes.

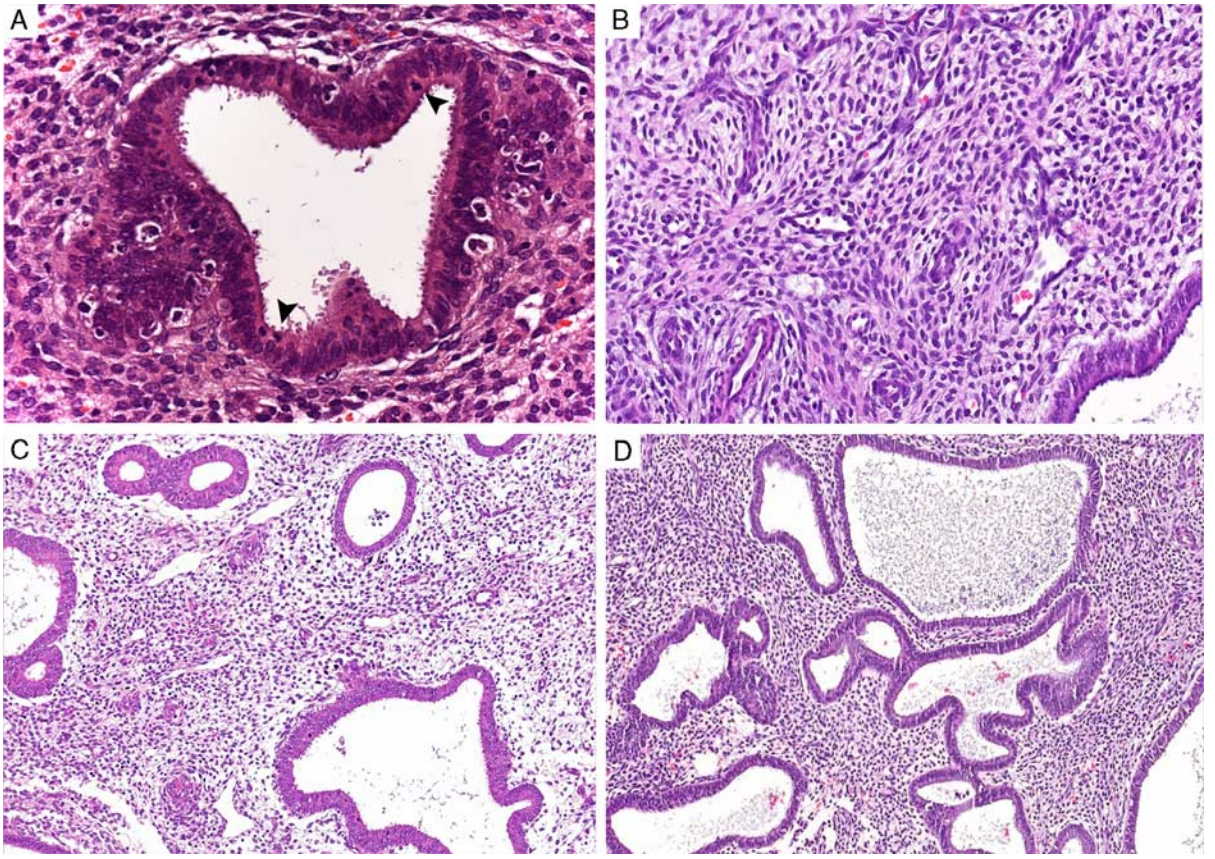

FIG. 1. Progesterone receptor modulators–associated endometrial changes in a cystically dilated endometrial gland lined by a cylindrical epithelium with basal nuclei and abundant cytoplasm. Both mitoses (arrowheads) and numerous apoptotic bodies coexist (A). Fibroblastic type stroma with a vascular network as a substrate of hysteroscopic chicken-wire appearance (B). Marked stromal edema and cystically dilated progesterone receptor modulators–associated endometrial changes glands (C). Glandular complexity but lacking atypical features may occur occasionally (D).

found in 27 of the surgical specimens removed 4 wk after cessation of treatment, 9 in specimens after 5 to 12 wk, and 5 after 12 wk.

PAEC

Histology and Definition

Fifty-nine cases had PAEC, which were defined as epithelial glandular changes of irregular or cystic endometrial glands showing a flattened secretory-like epithelium with isolated vacuolation and coexisting mitoses and apoptotic figures (Fig. 1A). Stroma was often edematous with a fibroblastic appearance resembling the stroma of endometrial polyps. Vessels were arranged in a net-like fashion with dilated sinuses (Figs. 1B, C); however, no arterioles with thickened muscularis were found. Cystic glands were rarely confluent and occasionally had irregular contours (Fig. 1D). PAEC occurred in 2 distinct forms: focal and diffuse.

Focal PAEC

A total of 51 cases presented as a cyclic endometrial mucosa with 3 or more isolated cysts with characteristic epithelial changes (Fig. 2A). These endometria were not associated with significant increase of the endometrial thickness. It is worth noting that in 12 cases, isolated cystic PAEC occurred in the foci of adenomyosis (Fig. 2B), being evident on the macroscopic study. Focal PAEC occurred in 22 cases of secretory endometria, 26 of proliferative type and only 3 atrophic.

Relationship Between Focal PAEC Histology, UPA Dosage, and Time Elapsed After Discontinuation of Treatment

Thirty-eight patients had received just 1 cycle, 11, two cycles, and only 2, three cycles. Thirty-one of the surgical specimens were removed 4 wk after ending the treatment, 15 after 5 to 12 wk, and 5 after 12 wk.

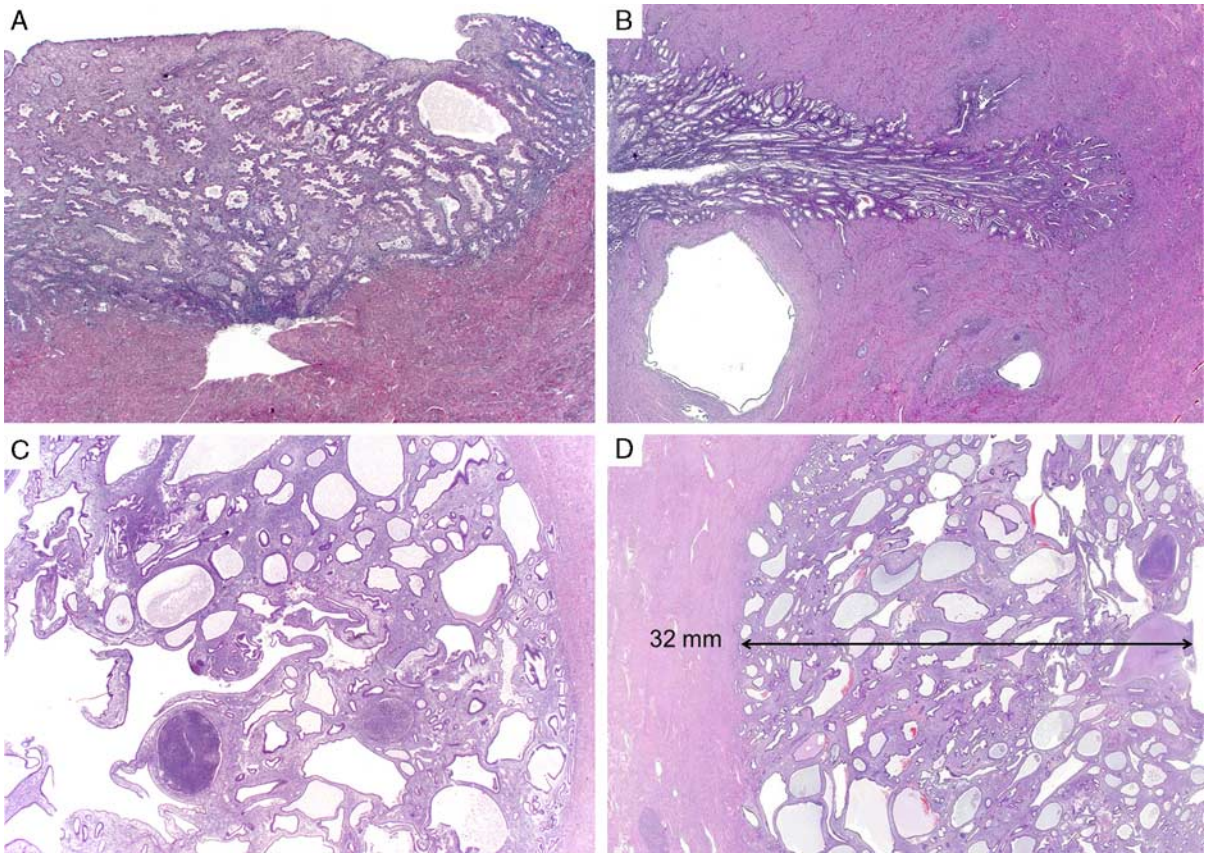

FIG. 2. Low power appearance of focal progesterone receptor modulators–associated endometrial changes (isolated cyst) in a secretory endometrium (A). Progesterone receptor modulators–associated endometrial changes cysts involving adenomyosis (B). Diffuse progesterone receptor modulators–associated endometrial changes with consistent cystic changes and marked increase (32 mm) of endometrial thickness (C and D).

Diffuse PAEC

Diffuse PAEC was found in only 8 patients, all presenting with uterine bleeding. Macroscopically, PAEC were striking, revealing an endometrium transformed into a thick white-yellow spongy cushion (Fig. 3A) obliterating the endometrial cavity, but not involving the endocervix. On cut section (Fig. 3B), a honeycomb of cysts was present through the full endometrial thickness.

Histologically, PAEC involved the full thickness of the endometrial lining. Cystic changes with a marked variation of diameter and contours were widespread (Figs. 2C, D). These, together with expanded stromal component, greatly increased the thickness of the endometrium, which ranged from 6.2 to 32 mm with an average of 11.8 mm.

Relationship Between Diffuse PAEC Histology, UPA Dosage, and Time Elapsed After Discontinuation of Treatment

Four patients had received just 1 cycle, 2, two cycles, and only 2, three cycles. All of the surgical specimens (8) were removed within 4 wk after ending the treatment.

Focal tubal metaplasia occurred in 41 cases and was found in association with 20 cases with normal histology. In PAEC, it occurred in 18 instances of focal and in 3 diffuse PAEC.

Leiomyoma histology was not specifically analyzed, but it was otherwise unremarkable, except for a substantial increase of interstitial fibrosis.

DISCUSSION

This study describes, for the first time in hysterectomy specimens, the endometrial changes occurring during treatment with a progesterone receptor modulator: UPA.

All previous studies dealing with a sizable number of patients have been performed on biopsy material. The limitations of a small tissue sample, particularly in aspiration biopsy, hinder an evaluation of the real

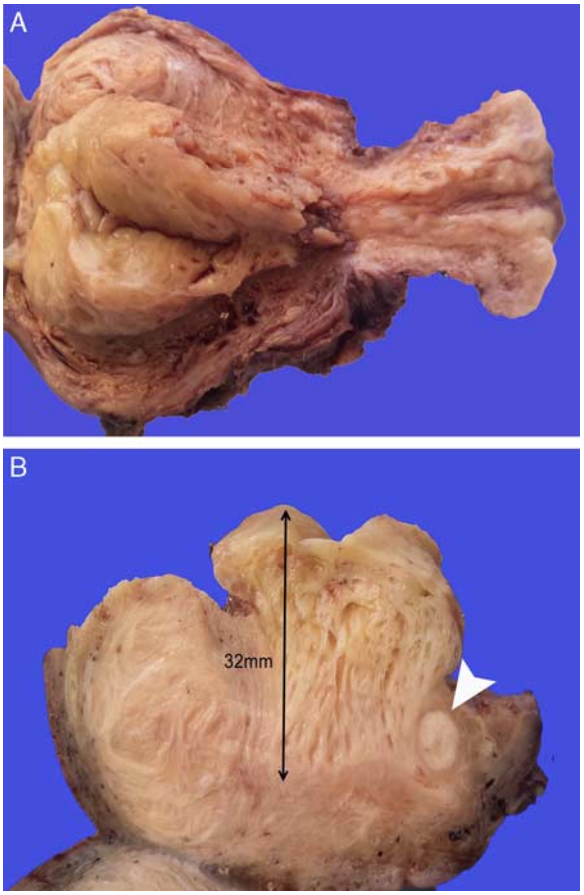

FIG. 3. Macroscopic appearance of diffuse progesterone receptor modulators–associated endometrial changes. The endometrium appears transformed into a thick cushioned lining (A). On cut section, the thickened mucosa reveals a spongy tissue with numerous cysts. An involutive leiomyoma is seen (arrowhead) (B).

extent and distribution of PAEC: a complex set of histopathologic lesions that are associated with treatment with UPA and other SPRMs (8), but may also occur spontaneously (4,9). The observation of whole endometria in hysterectomy specimens and in the lining of submucous leiomyomas has allowed us to appreciate better the topography, extent, and distribution of lesions. These findings provide a structural reference for a correlation with ultrasonograms.

Cases were studied in our centers from the introduction of UPA treatment for uterine leiomyomas to date. We analyzed our material during a period of 3 yr in order to ascertain the impact of the novel diagnosis of PAEC in routine practice. The majority of our cases (66/100) were operated within the first 4 wk after discontinuation of treatment. The observation during this early time slot provided us with a more accurate picture of the character and extent of actual PAEC, as in most studies surgery and subsequent histopathologic analysis are performed at a later date (10), thus eluding an interpretation of fresh, active lesions.

Not all patients treated with UPA react in a similar way. Indeed, the number of normal cyclic endometria found in UPA-treated patients in the biopsies taken 4 wk after the end of the treatment varied between 40% and 45% (2,11), depending on the type of treatment, using either a daily dose of 5 or 10 mg. In our study, the proportion of normal cyclic endometria (41/100) was similar.

In this paper, we identified the endometrial distribution of PAEC. Their most frequent presentation, occurring in half of the cases, was as a focal lesion consisting of isolated or clustered cysts within normal cyclic endometria that were lined by an epithelium with pseudosecretory features, displaying both mitoses and apoptosis. Only rarely (8/100) did PAEC occur as a diffuse, widespread change involving the full thickness of the endometrium. Consequently, we classified them as focal or diffuse PAEC.

The macroscopic appearance of PAEC has not been previously reported. Although focal PAEC have a similar appearance to normal endometria, diffuse PAEC consist in a striking diffuse cushioning of the endometrium that, on cut section, has a honeycomb texture. Cysts with characteristic epithelia and a marked stromal expansion contribute to an increase in its thickness. We observed that this stromal component has an edematous, fibroblastic morphology resembling the stroma of endometrial polyps —a fact that has not been described in biopsy studies. In contrast with previous studies, we did not observe any increase of muscular arteriolar proliferation. Chicken-wire capillaries and sinuses were, however, a frequent finding. Although tubal metaplasia was considered to be part of PAEC, in our cases it occurred with equal frequency in both normal endometria and PAEC.

Lesions, particularly those of diffuse PAEC, may represent a diagnostic challenge because of their complex cystic architecture and epithelial changes, as they have an inexplicable coexistence of secretory, proliferative (mitoses), and involutive (apoptosis) phenomena. Once the lesional pattern of PAEC is known, it is easy to differentiate it from both simple hyperplasia and polyps.

Diffuse PAEC is rare but occurred in a similar proportion in patients with one or more (up to 3) cycles. Thus, it does not seem to be related to the number of cycles of UPA treatment but rather reflects a yet unexplained threshold of endometrial susceptibility.

It is striking that thick, extensive lesions can undergo such a remarkable involution during the short period of 12 to 17 wk after discontinuation of treatment (1,3,12), irrespective of the number of cycles. This is also confirmed in hysteroscopy (13). In the present study, involution of lesions was nearly total, with only isolated focal lesions in the small group of patients (10%) who were operated after 12 wk. Between 5 and 12 wk, only 15 cases of focal and none of diffuse PAEC were found. It is significant that all cases of diffuse PAEC were found in the first 4 wk after discontinuation of treatment, with no cases found in uteri operated after 5 wk subsequent to treatment. It would seem that hysterectomies performed after 12 wk show a low incidence of PAEC.

It is noteworthy that PAEC cysts also occur in adenomyosis, being even larger than the focal PAEC lesions that occurred in the endometrial lining. These changes were present in all uteri with adenomyosis (12/100) and similar to those occurring in endometriosis (7).

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