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## Three-month treatment with ulipristal acetate prior to laparoscopic myomectomy of large uterine myomas: a retrospective study



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### ABSTRACT

**Objective:** To assess the usefulness of 3-month treatment with ulipristal acetate (UPA) before laparoscopic myomectomy of large uterine myomas.

**Study design:** This retrospective analysis of a prospectively collected database included women of reproductive age requiring laparoscopic myomectomy with the following characteristics: FIGO type 3, 4 or 5 myomas; largest diameter of the main myoma  $\geq 10$  cm; number of myomas  $\leq 3$ ; largest diameters of the other myomas  $\leq 5$  cm (second myoma) and  $\leq 3$  cm (third myoma). Patients either underwent direct surgery (group S) or were treated before surgery with UPA for 3 months (group UPA).

**Results:** The mean ( $\pm$ SD) intraoperative blood loss was lower in group UPA ( $507.1 \pm 214.9$  ml) than in group S ( $684.2 \pm 316.8$ ;  $p = 0.012$ ). The total operative time was lower in group UPA ( $137.6 \pm 26.8$  min) than in group S ( $159.7 \pm 26.8$  min;  $p < 0.001$ ); there was no significant difference in the suturing time between the two study groups ( $p = 0.076$ ). Hemoglobin drop was lower in group UPA ( $1.1 \pm 0.5$  g/dl) than in group S ( $1.3 \pm 0.7$  g/dl;  $p = 0.034$ ). Six patients in group S and no patient in group UPA required postoperative blood transfusions ( $p = 0.031$ ). Complications were not different between the two groups ( $p = 0.726$ ). Moreover, preoperative treatment with UPA caused a significant increase in hemoglobin levels ( $11.9 \pm 1.6$  g/dl) compared with baseline ( $9.1 \pm 1.1$  g/dl;  $p < 0.001$ ).

**Conclusion:** A 3-month treatment with UPA before laparoscopy for large uterine myomas decreases intraoperative blood loss, hemoglobin drop, postoperative blood transfusion and length of surgery.

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### Introduction

When compared with laparotomic and minilaparotomic techniques, laparoscopic myomectomy (LM) improves intraoperative blood loss, postoperative hemoglobin drop, length of hospital stay and postoperative pain [1–4]. Preoperative hormonal treatment of uterine myomas aims to correct preoperative anemia, decrease the vascularization of the myomas, decrease the intraoperative blood loss and ideally the volume of the myomas. This treatment may be advantageous in all patients undergoing LM but particularly in those with large and/or multiple myomas which are at higher risk of intraoperative hemorrhage and need of blood

transfusion. Nowadays, LM can be performed even in woman with large uterine myomas [5].

Ulipristal acetate (UPA) is a selective progesterone receptor modulator that is used for the treatment of uterine myomas [6]. It effectively control heavy menstrual bleeding and shrinks the myomas [7–9]. The activity of UPA is based on several mechanisms. UPA has a direct action on uterine myomas by inhibiting cell proliferation [10,11], inducing apoptosis [10,11], inhibiting collagen synthesis [12], stimulating extracellular matrix degradation [11,12], and decreasing the expression of growth and angiogenic factors [13]. UPA has also a direct effect on the endometrium, which allows to rapidly stop the bleeding. Finally, UPA acts on the pituitary gland inducing amenorrhea by inhibiting ovulation and maintaining mid-follicular levels of estradiol [6].

Scanty evidence is available on the perioperative outcomes of women receiving preoperative treatment with UPA. While some studies assessed the use of UPA prior to hysteroscopic

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myomectomy [14–16], surprisingly, only one case report described the use of UPA prior to LM [17]. Hence, this study aimed to assess the usefulness of 3-month therapy with UPA prior to laparoscopic excision of large uterine myomas.

## Materials and methods

### Study population

This study was based on a retrospective analysis of a prospectively collected database that included women who underwent LM because of heavy menstrual bleeding caused by uterine myomas. The pictorial blood-loss assessment chart (PBAC) was used to estimate uterine bleeding [18]. This instrument is a self-administered pictorial chart that takes account of the number of sanitary pads and tampons used, and the degree to which each individual item is soiled with blood, passage of blood clots and episodes of flooding. The one-month PBAC score was calculated from the addition of daily PBAC scores for 28 days. A PBAC score >100 during the first eight days of menstruation was considered heavy menstrual bleeding.

Before surgery, women included in the database gave written informed consent to the use of their clinical data for scientific purposes. The Ethics Committee approval was not requested because this was a retrospective analysis of data prospectively collected for the clinical follow-up of patients.

The study included premenopausal women who underwent LM because of myomas with the following characteristics: main myoma FIGO [19] type 3, 4 or 5 with diameter  $\geq 10$  cm (first myoma); presence of  $\leq 3$  myomas; main diameters of the other myomas (FIGO type 3, 4, 5 or 6)  $\leq 5$  cm (second myoma) and  $\leq 3$  cm (third myoma). Exclusion criteria for the study were: previous uterine surgery; previous uterine artery embolization or endometrial ablation; additional conditions requiring surgical management (i.e., endometriosis); use of hormonal drugs in the 6 months before the administration of UPA or before surgery; history of myoma treatment with UPA. The following exclusion criteria were used for prescribing UPA: refusal to accept changes in the menstrual cycle; endometrial hyperplasia or endometrial polyps; history of endometrial, cervical, ovarian or breast cancer; undiagnosed vaginal bleeding; osteopenia or osteoporosis; history of seizure disorders, thromboembolic or cerebrovascular events, and relevant systemic diseases.

Patients underwent either direct surgery (group S) or received 3-month preoperative therapy with UPA (5 mg/day orally, Esmya; Gedeon Richter, Budapest, Hungary; group UPA). UPA treatment was started within the first four days of the menstrual period. Treatment with UPA was offered to all patients requiring LM after the approval of UPA in our country. Patients included in groups S either underwent surgery prior to UPA approval and refused other hormonal therapies (between September 2013 and October 2014) or refused preoperative treatment with UPA after its approval in our country (between November 2014 and March 2016). Patients were informed that UPA decreases the volume of uterine myomas [7–9] but no data is available on the use of UPA prior to LM; they were informed of the adverse effects of UPA. Patients received iron and ascorbic acid supplementation (Sideral Forte, Pharmanutra Srl, Pisa, Italy; two capsules per day). Patients treated with UPA were requested to report the adverse effects arising during the use of the drug.

### Objectives of the study

The primary outcome of this study was to assess whether UPA decreases the intraoperative blood loss. The secondary outcomes were to compare the operative outcomes and the incidence of

complications between group S and group UPA. The tertiary objectives were to record the changes in preoperative hemoglobin levels caused by UPA and to describe the adverse events arising during the use of UPA.

### Evaluation of myomas and assessment of outcomes

Uterine myomas were assessed by transvaginal ultrasonography (TVS) (Voluson E6, General Electric Medical Systems, Milwaukee, USA) on the day of surgery in both study groups and within 2 week before starting the therapy in group UPA. Virtual organ computer-aided analysis was used to evaluate the volume of the myomas (VOCAL, General Electric Medical Systems, Milwaukee, WI, USA) [14,20]. The sum of the volume of all the myomas affecting each uterus was defined as total myoma volume.

Patients included in group S completed the PBAC in the month before surgery; patients included in group UPA completed the PBAC before starting the therapy and during the treatment period.

The videos of the surgical procedures were reviewed. The duration of the operation was measured from the incision of the skin until the last suture of the skin. The time required to suture the hysterotomies was defined as suturing time.

In patients receiving preoperative UPA, changes in hemoglobin level ( $\Delta\text{Hb}_{\text{UPA}}$ ) caused by treatment were calculated ( $\Delta\text{Hb}_{\text{UPA}} = \text{Hb}$  measured on the day before surgery – Hb measured before starting treatment with UPA). At the end of surgery, all visible blood and irrigation fluid was removed from the abdominal cavity; the intraoperative blood loss was estimated measuring the quantity of blood in the suction bottle at the end of surgery (total volume of fluid in the suction bottle – volume of the irrigation fluid used during surgery). The drop in hemoglobin level was calculated as the change in hemoglobin ( $\Delta\text{Hb}_S$ ) level caused by surgery ( $\Delta\text{Hb}_S = \text{Hb}$  measured on the day before surgery – Hb on the day after surgery).

The complications of surgery were recorded.

### Surgical technique

All surgical procedures were executed under general anesthesia with endotracheal intubation. Two skilled senior gynecologic endoscopists (S.F. and F.A.) performed the laparoscopies as previously described [2,20,21]. The surgeons were aware of the use of preoperative hormonal therapy. In group UPA surgery was performed within two weeks from the completion of the hormonal treatment. During surgery, the uterus was moved by using a uterine manipulator. The uterine wall and the pseudocapsule of the myoma were incised by using a unipolar hook electrode in order to identify the cleavage plane. A myoma drill was used to fix the myoma that was enucleated by a combination of traction with countertraction performed using Manhes forceps or anteversion and lateral movements of the uterus. Significant bleeding during myoma enucleation was controlled by bipolar coagulation. Myometrial edges were sutured in multiple layers using 1–0 absorbable polyglactin sutures (Vicryl; Ethicon Inc., Sommerville, NJ). When the uterine cavity was opened, the endometrium was sutured using 3–0 absorbable suture (Vicryl; Ethicon Inc., Sommerville, NJ). Electromechanical morcellation inside a plastic bag was performed to remove the myomas.

### Statistical analysis

The normal distribution of continuous data was assessed by the Kolmogorov–Smirnov normality test. Normally distributed data are presented as mean  $\pm$  standard deviation, otherwise, as median and interquartile range. The Student's *t* test was used to compare normally distributed continuous variables while the

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