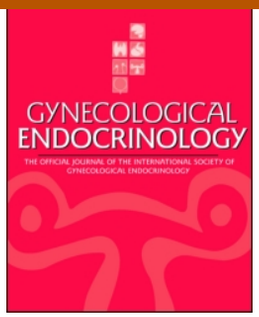

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ORIGINAL ARTICLE

Ulipristal acetate in symptomatic uterine fibroids. A real-world experience in a multicentric Italian study

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ABSTRACT

Surgery is the most frequent treatment in women with symptomatic uterine fibroids. A new medical approach with ulipristal acetate (UPA) has been suggested. The aim of this study was to provide data on effectiveness and safety of UPA in premenopausal women with symptomatic uterine fibroids. This was a multicenter retrospective cohort study. Data on all consecutive premenopausal women with symptomatic uterine fibroids referred to three Italian centers were included in a dedicated merged database. Women aged 18–55 years, who received pharmacologic therapy with UPA 5 mg orally once a day, were included in the study. The primary outcome was the percentage of women who underwent surgery after UPA treatment. One hundred and forty-two premenopausal women with uterine fibroids were included in this study. The mean age was 43.2 years. Eighty-one (57.0%) of 142 women treated with UPA had only medical treatment and did not undergo surgery. Surgical treatment occurred in 70, 23, 32, and 8% of the women who received one course, two courses, three courses, or four courses, of UPA treatment, respectively. The incidence of side effects was 10.6%. The effectiveness and safety of repeated UPA treatment courses in reducing number of women requiring surgery is confirmed by real-world data.

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Ulipristal; assisted reproductive technology; myoma; anemia; myomectomy

Introduction

Uterine fibroids, myomas, or leiomyomas are benign tumors, the most common of the female reproductive tract. Careful follow-up can be performed in asymptomatic women, or in those with mild symptoms [1–3].

The most frequent symptoms of uterine fibroids are abnormal vaginal bleeding, pain, and abdominal pressure [3,4]. Prophylactic therapy is usually not performed, except in cases of submucosal fibroids in women desiring pregnancy in order to reduce the risk of early pregnancy loss [4].

The goal of treating symptomatic women is to reduce symptoms [5,6], and surgery is the most frequent treatment [1,7–9]. Recently, a new medical approach with Selective Progesterone Receptor Modulators (SPRMs) has been suggested [9]. Short-term SPRMs administration led to improved quality of life, reduced menstrual bleeding with higher rates of amenorrhea compared to placebo [10]. Ulipristal acetate (UPA), a SPRM administered orally, is able to control excessive bleeding and to reduce significantly the size of the fibroids after 12 weeks treatment, and further with repeated intermittent courses [11]. Generally, patients, with heavy menstrual bleeding and myomas, selected and randomized in controlled trials do not fully represent the 'real world' because to reduce variability and to ensure quality of data adherence to a well-characterized protocol is usually requested.

Therefore, the aim of this study was to provide data on effectiveness and safety of UPA in premenopausal women with symptomatic uterine fibroids

Methods

This was a multicenter, observational, retrospective cohort study. Data on all consecutive premenopausal women with an ultrasound diagnosis of uterine fibroids, referred for myomectomy to three Italian Hospitals (Endoscopic Hospital, Freestanding Palagi Unit, Florence; University of Naples Federico II, Naples; and University of Cagliari, Cagliari) from October 1, 2014 to May 31, 2017 were included in a dedicated merged database.

Women aged 18–55 years, with symptomatic uterine fibroids, who received pharmacologic therapy with UPA, UPA 5 mg orally once a day were included in the study. Exclusion criteria were (a) postmenopausal women; (b) women received additional treatment (e.g. uterine artery embolization); and (c) women pretreated with gonadotropin releasing hormone (GnRH) agonists, combined hormonal contraception, or progestogens.

Outcomes

The primary outcome was the percentage of women undergoing surgical procedures after UPA treatment. The secondary outcomes were changes in fibroids volume before and after the pharmacologic treatment assessed by ultrasound, and changes in menstrual flow. For hysteroscopic surgery, we also planned to assess ease of delineating surgical planes between the myoma and the myometrium pseudocapsula. Surgeons performed two reports at the end of the surgical operations, assessing (1)

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difficulty in identifying the cleavage plan (a score from 0, no difficulty, to 10, highest difficulty); (2) the consistency of the myoma (a score from 0, soft, to 10 hard). Questionnaires were also performed regarding the difficulties in the execution of the intervention (0 = very bad and 10 = excellent), regarding the quality of the hysteroscopic vision (0 = none and 10 = maximum), regarding difficulty in dilating the cervical neck (0 = absent intraoperative bleeding and 10 = very abundant bleeding). Patient satisfaction and adverse treatment effects were also evaluated.

Statistical analysis

The estimated sample to be included in the study was about 150 patients to generate a 95% confidence interval with an amplitude of 0.17 when the sample proportion is 0.5 (calculations using the exact Clopper–Pearson formula). Given the observational and retrospective nature of the study, data on some variables are understandably incomplete, except for the variables related to the primary objective. Furthermore, given the observational and retrospective study design, the analysis was mainly descriptive. Appropriate statistical, parametric (Student *t*) and non-parametric (Wicoxon and McNemar) statistical tests were used to evaluate some study objectives and to compare data before and after medical and/or surgical therapy. Adverse events that emerged during drug therapy have also been reported descriptively (frequency, severity, duration, and measures are taken).

Results

Study population

During the study period 142 symptomatic premenopausal women with uterine fibroids, which met the inclusion criteria, were included in the study and analyzed.

The mean age was 43.2 years, ranging from 26 to 54 years. The mean BMI was 24, ranging from 17.5 to 35.1. The main features of menstrual bleeding were: regular menstrual cycle in 71.3%, irregular in 21.3%, other (polymororrhea, absent, and oligomenorrhea) 7.4%; menstrual bleeding duration: prolonged (>8 d) in 75.6%, normal (4.5–8.0 d) in 22%, short 2.4%; menstrual bleeding entity: abundant in 96.3%, other (normal and low) 3.7%; hemoglobin: median value 9.00 mg/dL (Table 1).

At the first visit 46 patients (92%) complained of pelvic pain, reported with a severity of pain (VAS 0–10) of 0–3 in 18.9% of cases, of 4–6 in 45.2%, of 7–10 in 35.9%, of which 9.4% was unbearable pain (VAS 10). The average pain severity score was 5.3.

The number of fibroids per patient at the first ultrasound was 1 myoma in 64% of cases, 2–3 myomas in 26% of cases, 4–6 myomas in 10%. The type of myomas, according to the FIGO classification, was for 21% submucosal, for 56% intramural, for 15% subserosal. The overall average volume of myomas at the first pretreatment visit was 98.6 cm^3 (43 cm^3 of median).

Regarding duration of UPA treatment, out of 142 women treated with 5 mg/die UPA, 60 (42.3%) received UPA for 1 course (3 months); 47 (33.1%) for 2 courses, 22 (15.5%) for 3 courses and 13 (9.2%) for 4 courses (Table 2).

Primary outcome

Eighty-one (57.0%) of 142 women treated with UPA had only medical treatment and did not undergo surgery. Surgical treatment occurred in 70, 23, 32, and 8% of the women who received one cycle, two cycles, three cycles, or four cycles, of treatment, respectively (Table 3).

Table 1. Characteristics of the included women at the first visit.

Characteristics	Values	*N* = patients
Age (years)	43.2 ± 8.4	142
BMI	24.0 ± 3.7	50
Irregular menstrual cycle	29 (21.3%)	136
Menstrual flow >8 d	96 (75.6%)	127
Menstrual flow abundant	105 (96.3%)	109
Hemoglobin mg/dL	9.00 ± 2.1	72

Data are presented as mean ± standard deviation or as number (percentage).

Table 2. Number of UPA courses received by patients analyzed.

	All patients	1 course UPA	2 courses UPA	3 courses UPA	4 courses UPA
N. Pts/%	*n* = 142 (100%)	*n* = 60 (42.3%)	*n* = 47 (33.1%)	*n* = 22 (15.5%)	*n* = 13 (9.2%)

Table 3. Number of women requiring surgery according to number of UPA courses received.

	Overall (n = 142)	1 course UPA (n = 60)	2 courses UPA (n = 47)	3 courses UPA (n = 22)	4 courses UPA (n = 13)
Surgery	61 (43.0%)	42 (70.0%)	11 (23.4%)	7 (31.8%)	1 (7.7%)

Secondary outcomes

During the study period, a variable number of ultrasounds (range 2–6) were made to the patients. Of the patients, 65% had two ultrasound reports, and 35% of the women had three or more scans. Regarding the effects of therapy on the volume of myomas in all patients who did not undergo surgery between the first and last ultrasound ($n = 132$): the average/median value of the volumes went from 102.4/43.6 to 83.9/28.3 cm^3, with an average reduction of −18% and a median of 35% ($p < .01$).

With regard to the intensity of the menstrual bleeding, in 85 women, 80 of them (94.1%) reported at the first visit an abundant bleeding (Table 1); at the last evaluation, only 22 patients (25.9%) still had abundant bleeding, 3 (3.5%) a poor bleeding, and the others 60 (70.6%) reported a normal bleeding ($p < .01$). With regard to the duration of the menstrual bleeding, in 102 women, 78 (76.5%) reported in the first visit a prolonged bleeding (menstrual bleeding >8 d); at the last visit, only 17 (16.7%) patients reported a prolonged bleeding and patients with normal menstrual bleeding duration went from 21.6 to 81.4% ($p < .01$).

Hemoglobin levels improved during treatment: in 72 of 142 women whose data were reported, about 50% had the median hemoglobin level less than 9 mg/dL at baseline; after UPA treatment only 25% of women had hemoglobin level less than 12 mg/dl.

Safety and tolerability

The following adverse effects were reported in 15 patients (10.6%), during treatment with UPA: 6.3% of experienced headache patients, 3.5% reported swelling/abdominal pain, 1.4% hot flushes and, 0.7% complained mood swing. All adverse events were mild to moderate (7 mild and 8 moderate), no severe event

was detected. Of the women, 97.6% were satisfied with the treatment.

Patient satisfaction score on therapy was reported in 81 patients. The acceptability of the therapy was good, in fact with a score ranging from 0 to 10 (0 = no satisfaction and 10 = maximum satisfaction), 97.6% of the patients declared a score > of 5 in terms of overall satisfaction, 14.8% a score between 9 and 10 and 49.4% a score between 7 and 8.

Hysteroscopic surgery outcomes

During hysteroscopic surgery, the separation of G1–G2 myomas from the myometrium was usually easy to perform using cold loops. All procedures were ended by slicing technique. The operation was considered complete when the fasciculate fibers of the myometrium (fovea) were visualized.

The endometrial aspect was hypotrophic in 84.6%, proliferative in 7.7%, with confluent cysts with a flaccid aspect in 3.8%, secretory 3.8%.

Questionnaires regarding the difficulty in identifying the cleavage plan were performed for 25 patients. With a score from 0 to 10 (0 = none and 10 = maximum) the average score was lower than 5 (score 4.4).

Questionnaires regarding the consistency of the myoma were performed for 27 women. With a score from 0 to 10 (0 = soft and10 = hard) the average score was 5.5, with no cases lower than 5.

Overall, in 96.4% there were no difficulties in the execution of the intervention, with an average score = 7.5 (0 = very bad and 10 = excellent) regarding the quality of the hysteroscopic vision; the average score was 3.6 (0 = none and 10 = maximum) regarding difficulty in dilating the cervical neck; the average score was 4 (0 = absent intraoperative bleeding and 10 = very abundant bleeding) regarding intra-surgical bleeding.

Discussion

Uterine fibroids are the most common benign uterine tumors in women, occurring in about 20–40% of those in fertility age. Current management includes surgical, either myomectomy or hysterectomy, or non-surgical approach [12,13]. Non-surgical approach includes medical treatment with hormonal or non-hormonal therapies, and radiological procedures, including uterine artery embolization [1]. Among medical treatments, SPRMs are a new class of drugs. SPRMs include UPA 5 mg tablets, [14] currently approved for preoperative treatment and for intermittent treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age. Due to its anti-progesterone properties, UPA has been shown to cause a reduction in uterine bleeding and fibroid size, leading to symptomatic improvement in women with fibroids who are planned for surgery [14]. Despite proven efficacy for fibroid symptoms, data on the effect of UPA in clinical practice is limited. Available literature focuses mainly on surgical outcomes of myomectomy [15]. Moreover, the effects of long-term treatment of UPA have not been extensively investigated in clinical practice so far [16].

Our study, evaluating efficacy and safety of UPA in real life, in women with symptomatic uterine fibroids, showed that treatment with UPA is an effective therapy in reducing number of women requiring surgery. The efficacy increases increasing numbers of UPA courses, up to four courses. In our cohort, surgical treatment occurred in 70, 23, 32, and 8% of the women who received one course, two courses, three courses, or four courses, of treatment, respectively. Therefore, repeated intermittent administration of UPA seems to maximize its potential benefits in terms of complete avoidance of surgery in more than 50% of women. The incidence of side effects was 10.6%, with headache being the most common one. Our study also showed that UPA was associated with significant reduction in myoma volume and improved menstrual symptoms. Moreover, hysteroscopic myomectomy was not negatively affected by presurgical treatment with UPA; in fact, 96.4% of the surgical operators did not report any difficulty in performing surgery.

Study limitations included the small sample size, but part of the reason of limited patients treated with repeated courses, depends on late introduction of the second indication of the drug in Italy in September 2016, incomplete electronic hospital records and the short follow-up. The retrospective non-randomized study design is the major shortcoming of the study.

In conclusion, the findings of this real-world study demonstrate the efficacy of more than one course of 5 mg UPA in bleeding control and fibroid shrinking and further confirm the use of repeated intermittent administration of UPA in avoiding surgery. Therefore, therapy with UPA may be offered as a safe and effective alternative to standard surgical approach in premenopausal women with symptomatic uterine fibroids. Large well-designed randomized controlled trials are needed to confirm our findings

Disclosure statement

The authors report no conflict of interest.

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