

# The role of Ulipristal Acetate in infertile women with submucous fibroids

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## Research

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## **Abstract**

**Background** The presence of submucous fibroids strongly impacts on IVF results, therefore, this patients should be considered for surgical or medical treatment. The aim of this study was to assess the role of Ulipristal acetate (UPA), a selective progesterone receptor modulator, in restoring uterine cavity deformation due to submucous fibroids, in infertile patients attempting an IVF treatment.

**Methods** Infertile patients with submucosal fibroid (Type 1 and Type 2 according to FIGO classification) were enrolled and received 1 to 3 treatment cycles of UPA, according to their response, as reflected by fibroid volume reduction and restoration of normal uterine cavity.

**Results** 26 patients underwent UPA treatment revealed a mean volume reduction of their fibroids of 41%. A total of 15 (57.6%) biochemical pregnancy were obtained, resulting in 13 (50%) ongoing pregnancy and 9 (34.6%) healthy babies were already delivered.

**Conclusion** Restoration of normal uterine cavity by UPA treatment prior to IVF treatment avoids surgery and enhances the pregnancy rate.

## **Background**

Uterine leiomyomas, or fibroids, are the most common form of benign uterine tumors occurring in 20–40% of women of reproductive age [1]. They are hormone-sensitive, smooth-muscle tumors with a wide heterogeneity in composition, size and number.

In the majority of cases, fibroids are asymptomatic, the diagnosis is incidental and need no intervention. However, third of cases represent with a variety of symptoms, depending on their location and size, and require treatment. The most common symptom is abnormal uterine bleeding, usually excessive menstrual bleeding with subsequent anemia, which could be life-threatening. Other symptoms include pelvic pressure, bowel dysfunction, urinary frequency and urgency, urinary retention, low back pain, constipation, dyspareunia and obstetrics complications [2] .

Infertility and recurrent miscarriages may also be symptoms of fibroids. Their anatomical location, specifically submucous and intramural fibroids, seems to be the most relevant factor affecting fertility and fertility treatments [1, 3, 4].

Fibroids can impair fertility through several possible mechanisms including: alteration of the local anatomy (anatomic distortion of the uterine cavity) with subsequent endometrial function modification [3]; functional changes, such as increased uterine contractility and impairment of the endometrial and myometrial blood supply [1]; and changes to the local hormone milieu which could impair gamete transport and/or reduce blastocyst implantation [5]. The type of treatment is guided by fibroid's characteristics (size, number and location), patient's age and whether the women desires to preserve fertility or not.

Submucous fibroids (Type 1 and 2 according to FIGO leiomyoma sub-classification system) [6] distorting the uterine cavity, negatively impact implantation rates, pregnancy outcomes and IVF treatments success [1, 3, 4, 7, 8]. Therefore, before starting IVF procedure, the resection of submucosus fibroids is strongly recommended [9]. Treatment of fibroids is mainly surgical and the gold standard for submucosal fibroids is hysteroscopic myomectomy, enhancing conception and live births with a pregnancy rate in infertile women ranging from 16–76.9% [1, 7, 9, 10].

Beside the surgical eradication, several medical therapies are now available. One of which is Ulipristal acetate (UPA), a selective progesterone receptor modulator (SPRM). UPA is effective in controlling excessive bleeding, reducing fibroids volume and has been proposed as a pre-operative treatment in those women with symptomatic myomas undergoing surgical therapy [11, 12]. Data on pregnancy achievement after UPA treatment are inconsistent and mainly based on case reports and small series, but it seems to enhance the chance of conception [13, 14].

Recently, the first case of infertile advance-age patient with large intramural fibroid, who conceived by IVF treatment following a course of Ulipristal was reported [15]. The patient underwent two fresh fertility preserving IVF cycles, with cryopreservation of 9 day-3 embryos, followed by a 12 weeks course of UPA (5 mg per day) and a subsequent frozen-thawed embryo transfer with her own previously cryopreserved embryos.

Prompted by the aforementioned information, we aimed to evaluate the efficacy of UPA in avoiding surgery and restoring uterine cavity deformation prior to IVF treatment, and whether UPA pretreatment may improve IVF cycle outcome.

## Materials And Methods

We conducted a prospective observational study between March 2017 to March 2018, including all couple referred to our infertility and IVF clinic with a diagnosis of submucosal fibroid distorting the uterine cavity.

The study was conducted at “Santa Maria alle Scotte” University Hospital, Department of Molecular and Developmental Medicine and it was approved by the ethical committee of the Siena University under the ID 10818 clinical protocol.

Women who met the following inclusion criteria were eligible: age between 20 and 38 years; body mass index (BMI) between 18 and 30 kg/m<sup>2</sup>; regular menstrual cycles of 25–35 days. Other inclusion criteria were: basal FSH less than 12 IU/L (cycle day 2–5); a total antral follicle count of 10–25 follicles; infertility resulting from tubal factors; unexplained infertility; and presence of both ovaries.

The first selection criterion was the presence of a submucosal fibroid with more than 3 cm diameter [9], which cannot be treated with one step hysteroscopic approach. Only those classified as Type 1 to Type 2, according to the FIGO classification [6] and distorting the uterine cavity were included.

The exclusion criteria were: more than 2 fibroids, other causes of uterine cavity abnormality such as uterine septum or Asherman syndrome, previous surgery for infertility, history of pelvic inflammatory disease, polycystic ovarian syndrome, clinical or ultrasound suspicious for endometriosis, and previous surgery for endometriosis.

Other major comorbidities such as diabetes, hypertension, bowel chronic diseases, rheumatologic diseases or male infertility were also considered as exclusion criteria.

All the women underwent pre-treatment transvaginal ultrasound in which the size of fibroids (the three major diameters) were recorded and a sonohysterography to assess the cavity distortion. After confirming the diagnosis, UPA tablets 5 mg (Esmya, Gedeon Richter, Italy) was prescribed and the patients started therapy at the beginning of the next menstrual cycle (1 tablet/day).

Every patient received a minimum of 1 cycle (84 days), and up to 3 cycle with a full menstrual cycle wash-out, between two consecutive cycles; blood was drawn monthly to assess the liver enzymes profile. This treatment and management is standard in our clinic.

Follow-up visits were carried out at the end of every cycle of UPA therapy: fibroids size was measured by transvaginal ultrasound and a sonohysterography was repeated. A normal uterine cavity at sonohysterography was considered the condition allowing to proceed to ART; otherwise, only if a reduction of the volume was detected, the patient has offered an extra UPA cycle. In case of no change in fibroid volume the patient was withdrawn from the study and referred to surgery.

Medical history was collected from our electronic database and data about previous pregnancy or surgery, ovarian stimulation, oocyte retrieval and ART details were recorded.

Menses were synchronized with combined oral contraception pills and ovarian hyperstimulation was carried out from the second day of the menstruation with a standard start dose of 225 IU of urofollitrophin hormone (uFSH).

The dose was adjusted based on follicle measurements and hormonal evaluation of estradiol (E2) and progesterone (P) at the first ultrasound examination on day 6 of the cycle and subsequently every 2–3 days. When follicles reached a mean diameter of 14 mm, GnRH antagonist was started and continued throughout the stimulation period.

Once at least one follicle reached a diameter of  $\geq 18$  mm and two additional follicles reached a diameter of  $\geq 16$  mm, 250 mcg of r-hCG (Ovitrelle; Merck Serono, Germany) was administered to trigger ovulation, and 34–36 h later oocytes were retrieved.

A maximum of two cleaved-embryos or blastocysts were transferred 2–5 days after oocyte retrieval.

Vaginal capsules of micronized 200 mg progesterone (three times/day) were administered from the day of oocyte retrieval and continued for at least 14 days after embryo transfer.

Biochemical pregnancy was defined as transiently positive  $\beta$ -hCG level not associated with the development of an embryo, while ongoing pregnancy was referred as a viable intrauterine pregnancy of at least 12 weeks duration confirmed on ultrasound scan.

Statistical analysis was performed using the Graph Pad Prism 6 software. T Student test for paired data with Welch correction was used and results were reported as mean and standard deviation (SD). A value of  $P < 0.05$  was considered statistically significant. Categorical outcomes were reported as percentages.

## Results

During the study period a total of 40 patients with infertility and a diagnosis of submucosal fibroid (Type 1 and Type 2) were referred to our fertility clinic, of whom 27 were enrolled in the study and received 1 to 3 cycle of UPA treatment, accordingly to the volume reduction and the effect of the fibroid on the uterine cavity. Patients' characteristics are showed in table 1.

Mean patients' age was 33.7 years (range 30-36). The mean number of fibroid per patient was 1.4; 15 patients had one fibroid while 12 had 2 fibroids (table 1). The mean diameter of the fibroids distorting the cavity was 5.5cm (ranging from 3.7 to 6.3 cm), while the mean volume was 65.4 ml (ranging from 48 to 107 ml).

The patients received a mean of 1.8 UPA treatment cycles leading to a mean 41% reduction in the fibroid volume (range 16 to 76%) (figure 1). Only one patient did not respond to UPA treatment and showed a volume augmentation of 9.2% and was therefore excluded from the study and referred to surgery after the first 3-month UPA treatment cycle.

Biochemical parameters are reported in Table 2: after UPA treatment patients showed a significant improvement in hemoglobin, hematocrit and follicle-stimulating hormone (FSH) values, with no changes in anti-mullerian hormone (AMH) values.

Amongst the 26 patients who underwent ovarian stimulation for IVF, a mean of 4.4 (2 – 7) oocyte per patient were collected; 3.4 (1-5) embryos were obtained and a maximum of 2 embryos were transferred. A total of 15 (57.6%) biochemical pregnancy were obtained resulting in 13 (50%) ongoing pregnancy and 9 (34.6%) healthy babies were already delivered (table 3).

No in-between group differences in the extend of fibroids volume reduction were observed between patients who conceived, either biochemical/ultrasound diagnosis of pregnancy or delivered, and those that did not. No adverse effects or liver enzymes alteration were recorded during the study period.

## Discussion

Our study shows that restoration of normal uterine cavity prior to IVF treatment by UPA treatment, improves pregnancy rate and may avoid surgery. The role of progesterone and its receptors has been

extensively studied during the last years as being decisive in promoting the growth of uterine fibroids, and has stimulated interest in modulating the progesterone pathways [16].

Selective progesterone receptor modulators (SPRMs) are drugs that exert agonistic or antagonistic effect on progesterone receptors and can modulate progesterone effect on different tissues [17]. UPA is a SPRM that block progestogen activity and is effective in reducing uterine fibroids volume. This effect lasts over time, without major side effects [17]. In line with previous publications, in our series there was a mean volume reduction of 41% and only one patient was referred to surgery because no fibroid size reduction was detected.

The advantages of UPA are rapid reduction of amount of bleeding in the vast majority of cases and a significant reduction in fibroid volume [9]. Christopoulos et al demonstrated that the presence of fibroids not distorting uterine cavity negatively affect clinical pregnancy (odds ratio, OR 0.62; 95% confidence interval, 95% CI 0.41–0.94) and live birth rates (OR 0.58; 95% CI 0.48–0.78) in patients undergoing their first IVF/ICSI cycle [18]. The presence of submucous fibroids strongly impacts on IVF results, therefore, this patient should be considered for surgical or medical treatment [4]. Data on UPA exposure before IVF is limited, except for some case reports focused on intramural fibroids [15, 18, 19]. Wdowiack et al. reported a case of pre-treatment with UPA before an ICSI procedure ending with conception and vaginal delivery of a baby [19]. Lo Monte et al report a case of multiple uterine fibroids with two fibroids distorting the uterine cavity, who were treated with three months UPA prior to hysteroscopic myomectomy, and followed for three more months. Nine months after a second cycle of UPA the patient underwent an IVF treatment [20]. Moreover, since the major disadvantage of myomectomy is the need for an optimal waiting period between surgery and subsequent fertility treatment, that might be as long as 3 months [21].

Orvieto et al has suggested that while counselling an advance-age patient with prominent intramural fibroid, the treatment of choice should be 1–3 IVF cycles, aiming to cryopreserve 5–10 embryos, followed by a 12 weeks course of Ulipristal and a subsequent FET with her own previously cryopreserved embryos [15].

The present study is the first series, where UPA has been used in patient with fibroids distorting the uterine cavity prior to IVF treatment, demonstrating an ongoing pregnancy rate of 50%. Furthermore, we didn't observe any complication during pregnancy, related to excessive growth of the fibroid. Pre ART UPA treatment does not impairs embryos quality or foetal morphology and the subsequent pregnancy did not affect fibroid size [19].

The limitation of our study is the lack of a control group; however, the literature is unanimous in proposing a preoperative treatment in patient undergoing hysteroscopic resection of large fibroids.

As described by Donnez in 2016, in case of fibroids greater than 3 cm, a preoperative treatment is advisable [9]. Pre-surgical UPA treatment for large and complex fibroid induces its shrinkage and

increases the rate of complete resection with a shorter surgical procedure, allowing the possibility of one time hysteroscopic resection [22, 23].

Our series suggest the pre ART UPA treatment, as a possible alternative to surgery, with a reasonable pregnancy rate and avoiding possible surgical complications.

In conclusion, the presence of submucous fibroids strongly impacts on IVF results, therefore, this patient should be considered for surgical or medical treatment. UPA therapy is efficient in restoring uterine cavity deformation and improving subsequent IVF outcome. Avoiding surgery is also crucial in infertile women. Further large randomized controlled studies are needed to confirm our observation and to further define patient selection criteria. These will aid both fertility specialists' counselling and their patients in tailoring the correct approach to submucosal fibroid, optimizing the results without losing time.

## List Of Abbreviations

AMH: anti-mullerian hormone; ART: assisted reproductive technology;  $\beta$ -hCG: Beta human chorionic gonadotropin ; BMI: body mass index; CI: confidence interval; E2: estradiol; FIGO: international Federation of Gynecology and Obstetrics; FSH: follicle-stimulating hormone; GnRH: Gonadotropin-Releasing Hormone; Hb: hemoglobin; Hct: hematocrit; ICSI: Intracytoplasmic Sperm Injection; IVF: in vitro fertilization; OR: odds ratio; P: progesterone; SD: standard deviation; SPRM: selective progesterone receptor modulator ; r-hCG: recombinant human chorionic gonadotropin; uFSH: urofollitrophin hormone; UI: international unit; UPA: Ulipristal acetate.

## Declarations

### Ethics approval and consent to participate

The study was conducted at "Santa Maria alle Scotte" University Hospital, Department of Molecular and Developmental Medicine and all experiments were performed in strict accordance with the local Ethics Committee. Informed consent was obtained from all subjects. The study was approved by the ethical committee of the Siena University under the ID 10818 clinical protocol.

### Consent for publication

All co-authors have seen and approved the final version of the paper and have agreed to its submission for publication. All patients signed informed written consent forms.

### Availability of data and materials

The datasets used and/or analysed during the current study is available from the corresponding author on reasonable request.

### **Competing interests**

The authors declare that they have no competing interests.

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### **Authors' contributions**

All authors participated in study design, execution, analysis, manuscript drafting and critical discussion. All authors read and approved the final manuscript.

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## Tables

**Table 1: Patients' characteristics**

<b>Patients' Characteristics</b>	
Age	33.72 ± 1.77
BMI	23.44 ± 1.86
Nulliparous	20 (74)*
Primiparous	7 (26)*
Previous miscarriage	14 (52)*
Number UPA cycle	1.8±0.58
Patients with one fibroid	15 (55)*
Patients with two fibroids	12 (45)*

Data are expressed as median ± Standard Deviation

\*Data are expressed as absolute number (percentage)

**Table 2: Patients' biochemical parameters**

<b>Patients' biochemical parameters</b>	<b>Before UPA</b>	<b>Before IVF</b>	<b>P value</b>
<b>FSH</b>	9.83 ±1.14	10.04±1.26	0.0034
<b>AMH</b>	1.15 ± 0.26	1.11±0.23	0.095
<b>Hb</b>	11.06 ± 0.66	11.51±0.50	0.0001
<b>Hct</b>	36.58 ± 1.47	37.11±1.19	0.0027

Data are expressed as median ± Standard Deviation

FSH: follicle-stimulating hormone; AMH: anti-mullerian hormone; Hb: hemoglobin; Hct: hematocrit

**Table 3: IVF outcomes**

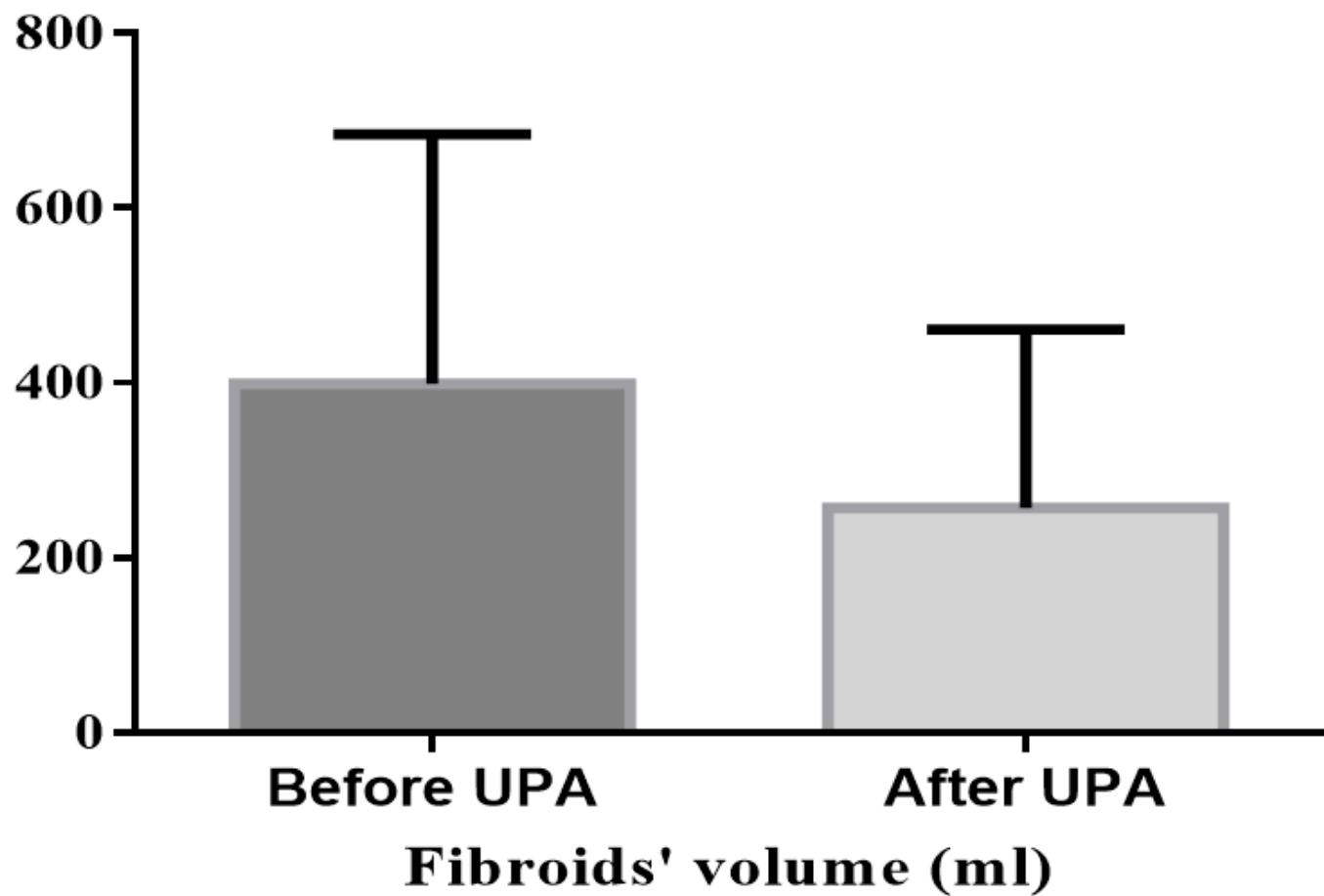
<b>IVF outcomes</b>
Oocyte retrieval
Number Embryos obtained
Biochemical pregnancy
Ongoing pregnancy
Healthy babies delivered

Data are expressed as median ± Standard Deviation

\*Data are expressed as absolute number (percentage)

## Figures

# **Fibroids' volume reduction**



**Figure 1**

Fibroids' volume reduction. UPA treatment led to a mean reduction in volume of the myoma impacting the cavity of  $41\% \pm 13.37$ . The volume before treatment was  $399.17 \pm 285.20$  ml and became  $257.02 \pm 203.83$  after UPA cycles