European Review for Medical and Pharmacological Sciences 2016; 20: 202-207

Ulipristal acetate prior to *in vitro* fertilization in a female patient affected by uterine fibroids: a case report

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Abstract. – OBJECTIVE: Uterine leiomyomatosis and especially submucosal myomas hamper the outcomes of Assisted Reproductive Techniques (ART). Even though surgical treatment eliminates gross anatomical anomalies, medical treatment should be encouraged to improve the overall structure of the uterus, thereby enabling ART.

CASE PRESENTATION: We report the case of an infertile female patient suffering from symptomatic uterine fibromatosis, who received 5 mg/day ulipristal acetate (UPA), a selective progesterone receptor modulator (SPRMs), for three months before and after hysteroscopic myomectomy. Uterine bleeding reduced on the eight days of treatment, with a subsequent improvement of pelvic pain. Under transvaginal ultrasound the uterus appeared globally enlarged with a diffuse leiomyomatosis of the myometrial layer. Saline infusion showed a markedly distorted cavity due two submucosal myomas (sized 31 × 24 mm and 21 × 19 mm, respectively) and one intramural myoma (37 × 34 mm). After three months the size of the myomas was reduced by 30-40%, allowing the hysteroscopic removal of the submucosal fibroids and the bigger intramural one. The smaller fibroids involving the myometrial layer were instead too diffused to be removed. At the conclusion of the subsequent cycle of UPA, the overall appearance of the cavity had improved, and the endometrial layer was regular, allowing the patient to undergo in vitro fertilization (IVF). There was no adverse effect related to treatment, and the endometrial biopsy did not reveal any histologic change.

CONCLUSIONS: UPA seems to have a triple effect: it ensures prompt symptom relief, it reduces the size of the myomas enabling surgery and it improves the morphology of the uterus.

Key Words:
Ulipristal acetate (UPA), Uterine fibroids, Myomas, Infertility, In vitro Fertilization (IVF).

Abbreviations

ART = Assisted Reproductive Techniques; GnRH agonist (GnRH-a); UPA = Ulipristal Acetate; SPRM = selective progesterone receptor modulator; IVF = In Vitro Fertilization; TVUS = Transvaginal sonography; MRI = Magnetic resonance; HyCoSy = Hysterosono-constrast sonography; PAECs = PRM-associated endometrial changes.

Introduction

According to several studies, voluminous intramural uterine fibroids and especially submucosal uterine fibroids are associated with reduced pregnancy rate and increased abortion rate[1]. Before undergoing Assisted Reproductive Techniques (ART), these myomas should be surgically removed.

When the patient is not eligible to surgery, treatment with GnRH agonist (GnRH-a) reduces the size of the myomas and allows to improve the echostructure of the uterus[2]. Ulipristal Acetate (UPA), a selective progesterone receptor modulator (SPRMs) allows to achieve the same clinical result, but its effect lasts longer[3] and hence it can represent an efficient alternative medical treatment, especially in the case of *In Vitro* Fertilization (IVF) candidates.

We have administered UPA to a symptomatic infertile patient suffering from uterine fibromatosis, who was a candidate to IVF. In the light of recent evidence[3,4], this new pharmacologic approach was supposed to reduce the volume of the fibroids, thereby, (1) controlling the symptoms (i.e. abnormal uterine bleeding and pain), (2) enabling surgery and (3) improving the whole anatomy of the uterus thereby optimizing the chances of a successful IVF.

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Case Presentation

A 32-year-old nulliparous female was referred to our clinic due to repeated episodes of menorrhagia, pelvic pain unresponsive to common analgesic treatments, asthenia and infertility for > 1 year. Due to severe asthenozoospermia of the partner, the patient was a candidate to IVF. Blood tests showed severe anemia (haemoglobin: 7.5 g/dL; hematocrit: 28%). Pelvic examination revealed a 14-week-gestation enlarged uterus. Transvaginal sonography (TVUS) and magnetic resonance (MRI) showed a globally enlarged uterus (60 × 93 × 58 mm) with several small fibroids involving the myometrium layer (Figure 1). Hysterosono-contrast sonography (HyCoSy) was scheduled in order evaluate both the distensibility of the uterine cavity and the tubal patency[5]. After saline infusion, the cavity appeared markedly distorted due to two submucosal myomas (sized 31 × 24 mm and 21 × 19 mm, respectively) (Figure 2) and an intramural myoma (37 × 34 mm) (Figure 3). Bilateral tubal patency was also proved. The patient was administered Ulipristal acetate, 5 mg/day for three months[6]. Both abnormal uterine bleeding and pelvic pain disappeared after eight days and two months of treatment, respectively. Under TVUS the endometrial layer appeared regular and was 9.3 mm thick (Figure 4), the two major submucosal myomas measured 21 × 15.6 mm and 13.6 × 12.5 mm, respectively, and the intramural one measured 24 × 22.1 mm. The volume of the fibroids was reduced of about 30-40%, as assessed by TVUS and Magnetic Resonance. The hysteroscopic myomectomy was then planned to normalize the uterine cavity profile. The surgical resection of the submucosal myoma was easily performed using a wire loop. The numerous and small intramural myomas were too diffused to achieve a complete removal during the 1-hour procedure resectoscopy. However, the biggest intramural myomas were removed 20 days after thanks to a second hysteroscopic procedure (Figure 5). An endometrial biopsy did not reveal histologic endometrial changes. The post-operative period was uneventful.

Subsequently, UPA was given for three further months in order to reduce the size of residual intramural myomas. Iron supplements were used continuously to treat anaemia. The levels of haemoglobin and haematocrit were completely recovered by the end of the treatment (haemoglobin: 12.1 g/dL; hematocrit: 42%). There was no adverse effect linked to UPA (i.e. headache, flushes, dizziness, discomfort, and tenderness in the breast).

A TVUS performed 9 months later showed a regular endometrial layer (endometrial thickness 6.2 mm) and an improved myometrial echostructure (Figure 6). This excellent result will allow the women to undergo IVF.

Discussion

According to literature, submucosal myomas have a negative impact on clinical pregnancy rate (RR 0.363, 95% CI 0.170-0.737) and are associated with an increased miscarriage rate (RR 1.678, 95% CI 1.373-2.051). There are no definitive data concerning the impact of intramural fibroids that distort uterine cavity on reproductive outcomes[7]. A systematic review performed by Pritts et al[7] confirmed the negative effect of intramural fibroids on reproductive outcomes in women undergoing ART. In particular, an RR of

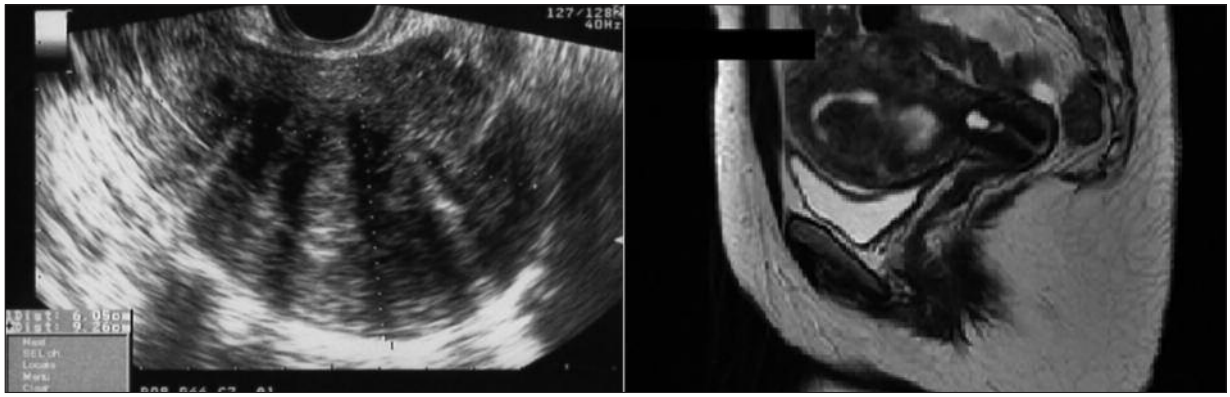

Figure 1. Overall appearance of the uterus before treatment, under TVUS (left) and MRI (right).

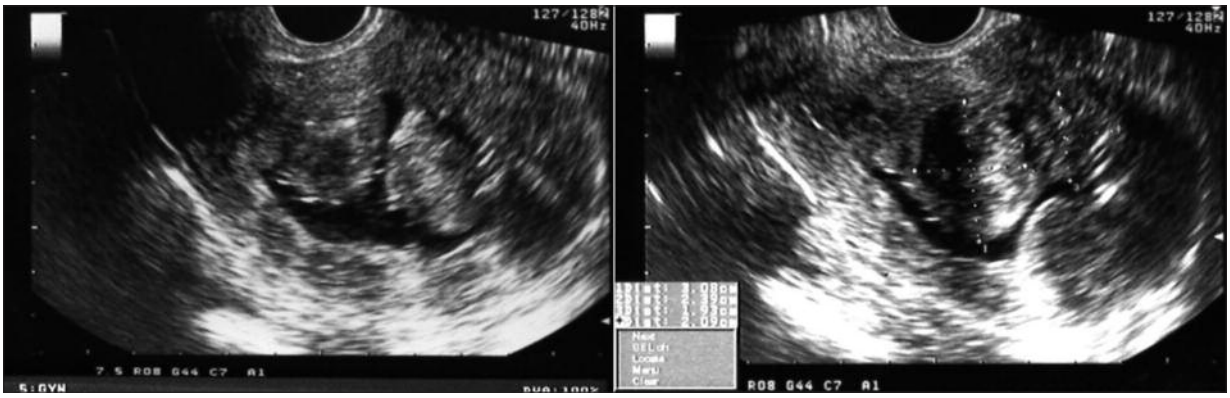

Figure 2. Two submucosal myomas distorting uterine cavity under HyCoSy.

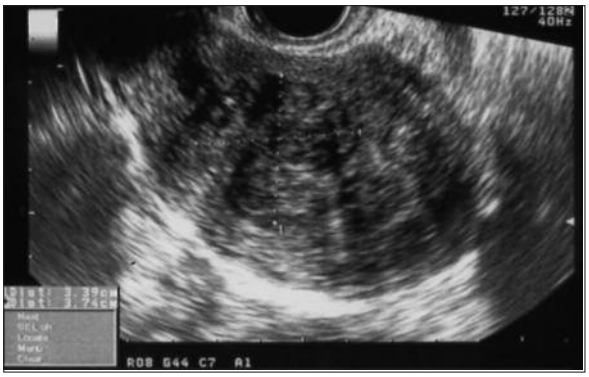

Figure 3. The largest intramural myoma under TVUS.

0.8 (95% CI: 0.69-0.94) for clinical pregnancy rate and an increased risk of spontaneous abortion with an RR of 1.7 (95% CI: 1.2-2.4) were found. Nowadays, the surgical correction of the uterine cavity is strongly suggested prior to ART. Myomectomy can be usually performed by hysteroscopy in the case of intracavitary or submucosal fibroids ≤ 4 cm while larger or multiple fibroids need a laparoscopic or laparotomic approach[8]. However, myomectomy could be responsible for specific surgical risks including pelvic (laparoscopic/laparotomic myomectomy) or intrauterine (hysteroscopic myomectomy) adhesions. This major risk should not be disregarded in the infertile patient, in which medical treatment represents a suitable alternative. However, a recent clinical practice guideline approved by the Society of Obstetricians and Gynaecologists of Canada (SOGC)[9] states that the exclusive role of the medical therapy for uterine fibroids is not applicable for the treatment of infertile patients. All medical treatments developed for the treatment of symptomatic women with uterine fibroids usually act by achieving the suppression of the ovulation, the reduction of oestrogens production and the disruption of the target action of oestrogens and progesterone (in particular interfering with the development of endometrium). All these effects are far from the aim of the treatment of an infertile woman, and a subsequent surgical approach should be always taken into account.

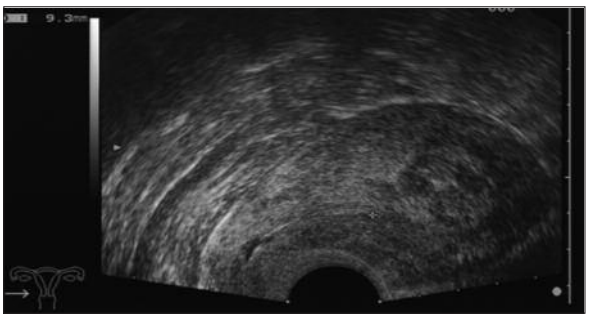

Figure 4. Overall improved uterine morphology and endometrial thickness after 3 months treatment.

For a long time, GnRH-a was the only available drugs for the treatment of fibroids. They are particularly useful in achieving the shrinkage of fibroids, the normalization of haemoglobin levels during the pre-operative phase and as a preoperative treatment, to allow a more conservative surgery. Such a medical management led to successful pregnancies in a symptomatic infertile patient affected by diffused uterine leiomyomatosis[2]. However, since the effect of GnRH-a is temporary, often incomplete and reversible, the window interval to apply ART is too short[9].

The European Medicine Agency recently approved Ulipristal Acetate (UPA), an oral selective progesterone-receptor modulator, for the

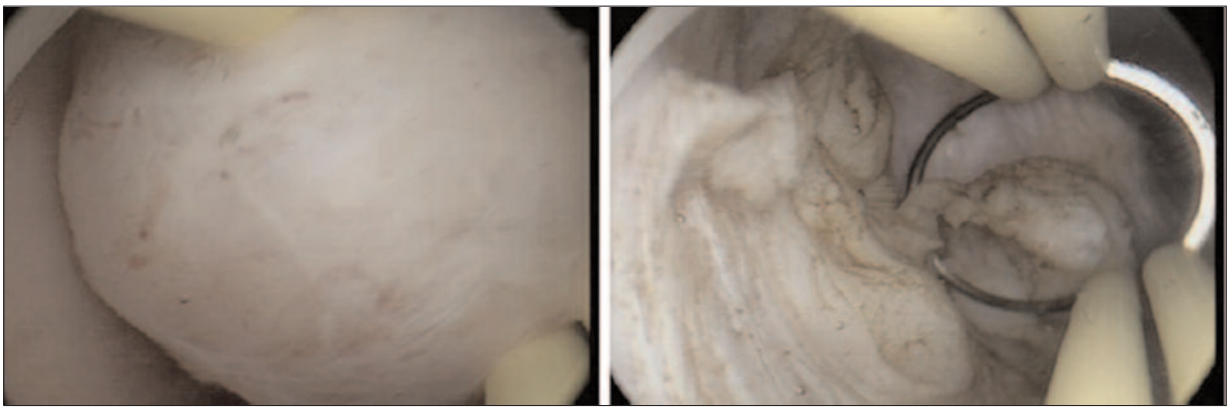

Figure 5. Uterine cavity before (left) and after (right) surgical removal of the myomas.

treatment of moderate and severe symptoms of uterine fibroids also in women of reproductive age[10]. According to clinical data, UPA shows several advantages: it is faster than GnRH agonists in reducing the fibroid-associated bleeding, it efficiently improves haemoglobin and hematocrit levels in anaemic patients, and it grants a significant reduction in the size of fibroids, which lasts for at least 6 months after the end of the treatment[3,4]. Furthermore, it has been recently observed that the volume of fibroids does not increase during pregnancies obtained after UPA[11]. According to literature, we reported a significant reduction in uterine bleeding on the 8th day of treatment, and the recovery of haemoglobin-hematocrit levels after six months. Furthermore, a 30-40% reduction in myoma size was demonstrated nine months after treatment, enabling surgery[3,4,6].

In addition to that, it has been proposed that UPA could restore the anatomy of a distorted uterine cavity by decreasing the size of myomas[12]. In fact, Levy et al[12] administered placebo, UPA 10 mg and UPA 20 mg, to three different groups of women affected by symptomatic fibroids that distorted the uterine cavity. Saline sonohysterography was performed at baseline and after three months of treatment. A normalized uterine cavity was demonstrated in 32% patients treated with UPA (both 10 mg and 20 mg), compared to 22% of the placebo group. However, this difference was not statistically significant.

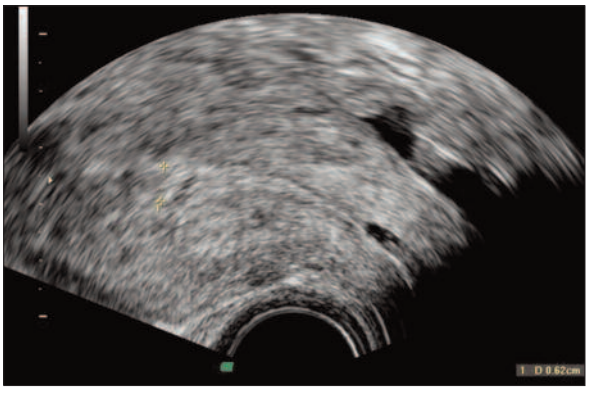

Figure 6. Final appearance of the uterus (after 3+3 months of UPA treatment + surgery).

On the ground of this evidence as well as the possibility to extend the treatment for three additional months[6,12], we scheduled a second cycle of UPA after surgery. We aimed at improving the overall profile of the uterine cavity through a direct effect on the small diffuse intramural myomas that could not be surgically removed.

The PEARL III and PEARL IV studies[6,13] confirmed the safety profile of UPA. The authors reported that the occurrence of adverse reactions did not increase during repeated treatment courses, allowing prolonged therapies in selected cases (as described in this case report).

To date, nineteen pregnancies occurred after UPA treatment. One case of spontaneous pregnancy and live birth has been recently reported by Monléon et al[14]. After a thorough retrospective analysis, Luyckx et al[11] concluded that 15 women became pregnant among PEARL II and PEARL III participants: 13 of them conceived after laparoscopic/laparotomic myomectomy, either spontaneously (n=7) or after IVF (n=6); in two cases, pregnancy was obtained without previous surgery.

Some experiments based on *in vitro* embryo systems have demonstrated that the addition of UPA to *in vitro* endometrial constructs does not

interfere with the endometrial receptivity and the implantation process of human embryos. Although UPA was initially developed for the purpose of the emergency contraception, it acts by delaying or inhibiting the ovulation and does not affect the gamete transport, the fertilization of oocytes, the embryo development and the embryo implantation[15,16].

It could be argued that UPA is not safe in women seeking pregnancy since it has been proved that it induces PRM-associated endometrial changes (PAECs), i.e. cystic changes and the increase in endometrial thickness[10]. Nevertheless, according to recent data, the endometrial thickness is restored to baseline levels after treatment discontinuation and thus PAECs are considered a reversible pharmacodynamic response[10]. In this clinical case, UPA determined a regular endometrial layer and an improved myometrial echostructure.

To the best of our knowledge, UPA has no adverse effect on pregnancy and fetus, and the observed miscarriages have been attributed either to the age of the patient or artificial conception[11]. Even though thickening of the endometrium has not been shown in our report (Figures 4 and 6) and endometrial biopsy was negative, the patient was suggested to wait three months before undergoing IVF.

Conclusions

Our findings support UPA as an efficient and safe treatment to reduce the size of uterine fibroids, thereby achieving symptom relief and enabling surgery for larger myomas. However, its shrinkage effect involves also the small myometrial myomas that distort uterine morphology, and the proven restoration of uterine anatomy maximizes the chances of a successful IVF. Further studies are needed to clarify (1) the role of UPA in IVF candidates; (2) whether such a medical management could avoid surgical procedures; (3) whether there are specific cases of uterine leiomyomatosis (localization, dimension, number of fibroids) that would be eligible to the sole medical treatment with UPA.

Patient Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Author Contributions

All authors provided substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data, and contributed to drafting the article and revising it critically for important intellectual content. All authors provided final approval of the version to be published, and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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