

DOI: <http://dx.doi.org/10.18203/2320-1770.ijrcog20172959>

Case Report

Ulipristal acetate (UPA) for fibroids–IVF outcomes following treatment with UPA after IVF failure: series of 2 case reports

Ashish R. Kale*

Asha Kiran Hospital, Nursing home and IVF Centre, Pune, Maharashtra, India

Received: 05 April 2017

Revised: 08 May 2017

Accepted: 18 May 2017

*Correspondence:

Dr. Ashish R. Kale,

E-mail: doctors.library123@gmail.com

Copyright: © the author(s), publisher and licensee Medip Academy. This is an open-access article distributed under the terms of the Creative Commons Attribution Non-Commercial License, which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

ABSTRACT

Uterine fibroids (also known as leiomyomas or myomas) are the most common form of benign uterine tumors. Fibroids are present in 5-10% of infertile patients, and may be the sole cause of infertility in 1-2.4%. The removal of fibroids by hysteroscopy and laparoscopy has now become the standard of care depending upon the size, number and location of fibroids in an infertile woman. Off lately, there is growing evidence of the crucial role of progesterone pathways in the pathophysiology of uterine fibroids due to the use of selective progesterone receptor modulators (SPRMs) such as ulipristal acetate (UPA). Here, we report a case series of 2 women, with fibroids, who were put on UPA prior to IVF. These women had at least one previous IVF failure. The pre and post UPA fibroid characteristics were compared to see the effect of the drug. IVF was done post 3 month UPA therapy. Both the women showed a drastic reduction in the fibroid size, increased distance from endometrial cavity, and successful post UPA IVF cycles. Safety of the drug has been proven in few recent trials, but the role of UPA in infertile women with fibroids, who have had previous IVF failure, has opened new horizons in this field.

Keywords: Fibroid, Infertility, Ulipristal acetate

INTRODUCTION

The failure to become pregnant after assisted reproductive techniques depends upon but is not limited to the ability of the embryo to implant and attach itself to the healthy endometrium. One of the commonest reasons why this can be hampered is presence of uterine fibroids, particularly sub-mucous and intra-mural ones. The distance between the fibroid and the endometrial cavity is the main factor which decides the impact on implantation and successful pregnancy outcome. Along with the distance from cavity, the size and number is also important. Even after conception, a pregnancy with a uterine fibroid is considered as a high-risk pregnancy.^{1,2}

There is increased rate of complications such as miscarriage, preterm birth, degeneration of fibroid, etc.³

The factors predisposing to uterine fibroids include age, African ancestry, obesity and nulliparity. Although studies performed to date have extended our knowledge on fibroid pathology, their Etiology has not been fully elucidated. With increasing population of sub-fertile and infertile women, the incidence of fibroid is increasing manifold. They are often even seen as an incidental diagnosis in these group of women, who are routinely subjected to an ultrasound screening before deciding the modality of treatment. Here, we report a case series of 2 women, with fibroids, who were put on UPA prior to IVF. These women had at least one previous IVF failure.

Uterine fibroids are present in approximately 70% and 80% of 50-year-old white and black women, respectively.⁴ Common symptoms include heavy menstrual bleeding and subsequent anemia, pelvic pain, dysmenorrhea, decreased quality of life, and reproductive dysfunction.

The optimal treatment for patients with symptomatic uterine fibroids and pregnancy desire remains unknown. It has been reported that myomectomy may improve fertility outcomes in women with submucosal and intramural fibroids. Nevertheless, there is still insufficient evidence from randomised controlled trials to establish the effect of myomectomy to improve fertility.⁴ On the other hand, current evidence is still insufficient to establish whether radiologic procedures represent a valid treatment option for women with symptomatic fibroids who want to preserve their fertility. Alternative medical therapies have limitations and are not considered a valid fertility-preserving treatment option. Uterine fibroid growth depends on the ovarian steroids estrogen and progesterone. Accordingly, oral progestin may promote fibroid growth and induce abnormal bleeding. Although the progestin-releasing intrauterine device would control heavy menstrual bleeding, it is hardly ever used in women with a deformed endometrial cavity by submucosal fibroids and also prevents pregnancy if used.

Therefore, the mode of management of fibroids in women who desire pregnancy depends on the size, number and location of uterine fibroids. The mainstay of management remains the surgical approach, when indicated.⁵

Further on, the results of studies conducted by Lai et al, Noor et al and Eze et al support the need for treating uterine fibroids before planned pregnancy to minimize the risk of complications described above.⁶⁻⁸

There are convincing data that progesterone and its receptors increase the proliferation activity of the cells in uterine leiomyomata, hence treatment with anti-progestins and progesterone receptor modulators seems to be reasonable.^{3,5}

Results of a successfully completed phase III clinical trials with the application of ulipristal acetate (UPA) (first-in-class selective progesterone receptor modulator--SPRM) have been published recently. UPA is a selective P receptor modulator (SPRM) that potently modulates P-receptor activity with proapoptotic/antiproliferative effects on fibroid cells and with pharmacokinetic properties supporting once daily dosing. Two short-term (3 months) randomized clinical trials showed that UPA effectively controls HMB and shrinks fibroids.^{9,10} After treatment cessation, menstruation usually returns within 4-5 weeks, but fibroid volume reduction can be sustained for up to 6 months.

Administration of 5 mg or 10 mg UPA daily has been shown to rapidly stop (within a week) excessive uterine

bleeding, reduce the volume of the three largest fibroids by -44.8% and -54.8% for UPA 5 mg and 10 mg, respectively. The effect on fibroid volume has been observed for up to 6 months after treatment cessation. It is also important that UPA restores patient Quality of Life scores to the level of healthy women and in the majority of patients resume menstruation and ovulation within one month after treatment cessation. When compared with the Gn-RH agonist (leuprolide acetate), UPA has controlled uterine bleeding faster and more consistently (7 days vs. 30 days), fibroid reduction for up to 6 months has been smaller for Gn-RH a (-16.5%) and UPA has shown a superior safety profile as estradiol levels are maintained in the mid-follicular range.

The presented results on the application UPA in the medical treatment of symptomatic uterine fibroids are very promising and gynecologists are given a new treatment option.

Ulipristal treatment has not shown any adverse effect on the quality of embryos in the morphological assessment during the ICSI procedure. Pregnancy does not induce changes in fibroid size following earlier treatment with ulipristal acetate.

However, since UPA exerts mainly antiprogestagenic effects on the endometrium, whether the ART protocols have to be modified, need further studies.

Also, in the studies so far, it has been observed that the effect of UPA is best-seen upto 6 months of cessation of the drug. Therefore, for women who require ART, it should be planned within this time frame.

Although larger and randomized control studies are required to further reinforce the fact, treatment of uterine fibroids is a promising treatment modality before planned pregnancy to improve fertility, enhance ART results, and to minimize the risk of obstetric complications.

Below we report 2 cases of pre-IVF Ulipristal, where uterine fibroid shrinkage was seen enabling ART without prior surgery for fibroids.

CASE REPORT

Case 1

31-year-old woman with primary infertility presented to us following one failed IVF cycle done outside 1 year ago for unexplained causes.

With us, the couple infertility work-up revealed normal study, except multiple uterine fibroids, which probably grew during the past 1 year when she did not seek any treatment.

The details of the fibroids have been tabulated in Table 1.

Table 1: Fibroid characteristics.

Region	Location	Type	Size (mm)	Remarks
Fundus	Posterior	Intramural	41 X 35 X 15 X 12	Indenting the endometrium at the fundus
Body of uterus	Posterior	Intramural	22 X 15 X 18 X 17	Just touching the endometrium, not indenting it
Body of uterus	Anterior	Intramural	20 X 15 X 13 X 12	Away from the endometrium
Body of uterus	Anterior left lateral	Intramural	18 X 15 X 8 X 8	Away from the endometrium

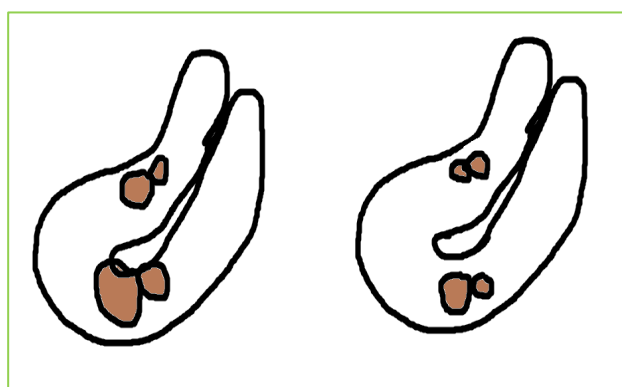
Table 2: Pre and post UPA comparison of fibroids.

Region	Location	Type	Pre-UPA Size (mm)	Post-UPA Size (mm)	Remarks
Fundus	Posterior	Intramural	41 X 35 X 15 X 12	29 X 25 X 15 X 9	6 mm away from the endometrium, not indenting the endometrium
Body of uterus	Posterior	Intramural	22 X 15 X 18 X 17	18 X 15 X 10 X 7	Away from the endometrium
Body of uterus	Anterior	Intramural	20 X 15 X 13 X 12	14 X 10 X 9 X 8	Away from the endometrium
Body of uterus	Anterior left lateral	Intramural	18 X 15 X 8 X 8	9 X 8 X 7 X 7	Away from the endometrium

The couple was counseled regarding the impact of cavity distorting, as well as the peripheral intra-mural fibroids. Both options were offered-laparohysteroscopic myomectomy and Ulipristal Acetate for 3 months. Not wanting to undergo surgery, the couple chose to take the medical management. The woman was put on 5 mg daily dose of Ulipristal acetate for 12 weeks.

A fibroid mapping was repeated after 12 weeks of UPA therapy.

The comparison of fibroids pre and post UPA are tabulated in Table 2.

**Figure 1: Pre and post UPA sagittal uterine sketch and fibroid mapping.**

To enable better comparison of the pre and post UPA effects on fibroids, a fibroid mapping and sketch was

done. The sagittal uterine sketch of the fibroids, pre and post UPA is shown in Figure 1.

After the UPA therapy cessation, she was taken for an IVF in the immediate cycle. 8 oocytes were retrieved, and 6 fertilized – 3 Grade A, 2 Grade B and 1 Grade C.

A fresh embryo transfer was done of the 2 Grade A embryos. The beta hCG value on Day 16 was 1600 mIU/mL. A single viable intra-uterine gestational pregnancy was documented at 6 weeks, which was followed upto 9 weeks, and is ongoing till submission of this paper.

Case 2

26-year-old lady with primary infertility. She had 2 failed IVF cycles-one done outside, and one with us. There was no obvious cause of infertility except multiple fibroid uterus, of which 2 fibroids were indenting the endometrial cavity. The woman was firmly against surgery – we had tried to convince her prior to our 1st IVF cycle too.

The fibroid mapping, case 2, has been tabulated in Table 3. Having refused surgery strongly, before going ahead with the 2nd IVF cycle, we offered her UPA with an aim to shrink the fibroids, and improve the distorted cavity.

She was also counseled that the isthmic fibroid, which abutted against the endometrial cavity, may cause difficulty while performing the embryo transfer.

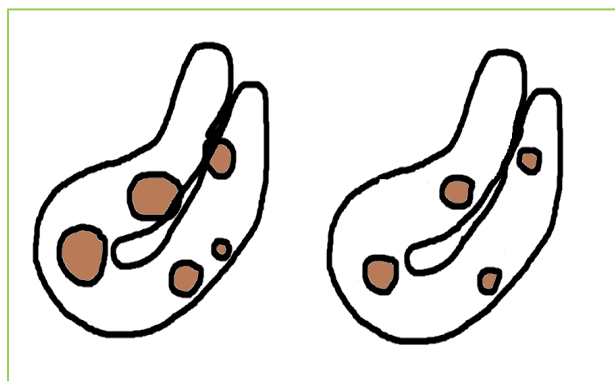
Table 3: Fibroid characteristics.

Region	Location	Type	Size (mm)	Remarks
Body of uterus	Anterior	Sub-mucous	35 X 33 X 12 X 12	Indenting the endometrium anteriorly
Isthmic	Posterior	Intramural	28 X 17 X 18 X 11	Abuts against the endometrium at the utero-cervical junction, causing a buldge, not indenting it
Fundal	Anterior	Intramural	33 X 30 X 11 X 9	Away from the endometrium
Body of uterus	Posterior	Intramural	18 X 15 X 8 X 8	Away from the endometrium
Body of uterus	Posterior	Intramural	9 X 8 X 4	Very small, peripheral intramural

Table 4: Pre and post UPA comparison of fibroids.

Region	Location	Type	Pre-UPA Size (mm)	Post-UPA Size (mm)	Remarks
Body of uterus	Anterior	Intramural	35 X 33 X 12 X 12	28 X 23 X 12 X 10	Away from the endometrium, no sub-mucosal element of fibroid post UPA
Isthmic	Posterior	Intramural	28 X 17 X 18 X 11	22 X 11 X 10 X 11	Away from the endometrium
Fundal	Anterior	Intramural	33 X 30 X 11 X 9	26 X 24 X 9 X 7	Away from the endometrium
Body of uterus	Posterior	Intramural	18 X 15 X 8 X 8	10 X 8 X 8	Away from the endometrium
Body of uterus	Posterior	Intramural	9 X 8 X 4	Cannot be seen	This fibroid could not be located post UPA

Not wanting to undergo surgery, the couple chose to take 5 mg daily dose of Ulipristal acetate for 12 weeks. A fibroid mapping was repeated after 12 weeks of UPA therapy. The comparison of fibroids pre and post UPA are tabulated in Table 4.

**Figure 2: Pre and post UPA sagittal uterine sketch and fibroid mapping.**

The sagittal uterine sketch of the fibroids, pre and post UPA, for case 2, is shown in Figure 2.

We had frozen embryos from her previous IVF cycle, and a FET was performed after a good lining was formed. Her beta hCG was positive on day 16, and a TVS at 6 weeks showed a single viable intra-uterine gestation, which has been carried till 14 weeks, when this article

was submitted. The pregnancy is ongoing and uneventful so far.

DISCUSSION

We present here a case series of 2 reports, in which UPA was given after a failed IVF cycle, and prior to the next IVF cycle. 12 weeks of UPA successfully reduced fibroid size and allowed the re-establishment of the morphology of endometrial cavity. Since Ulipristal acetate effectively shrinks fibroids and avoids risks of a new surgical procedure, it would allow an immediate attempt at conception at the end of treatment.^{4,5}

CONCLUSION

Although there is currently insufficient evidence to recommend medical treatment in the management of fibroids, UPA seems to be a novel and promising option, especially for infertile women who refuse to undergo surgery inspite of the fibroids distorting the cavity, and for those with fibroids who shall undergo IVF.

It has shown future promise in our small case series, however further, well designed RCTs are needed. Although no pregnancy-related complications or teratogenic effects have been reported to date, further series are required in order to establish the safety of ulipristal acetate as a treatment of symptomatic fibroids prior to IVF and pregnancy.

In infertile women, appropriate evaluation and classification of fibroids, particularly those involving or suspected to be involving the endometrial cavity is essential. Our findings support UPA as an efficient and safe treatment to reduce the size of uterine fibroids. 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

- The role of UPA in IVF candidates
- Whether such a medical management could avoid surgical procedures
- Whether there are specific cases of uterine leiomyomatosis (localization, dimension, number of fibroids) that would be eligible to the sole medical treatment with UPA
- Any detrimental effect of UPA on endometrial phase hampering IVF response.

Funding: No funding sources

Conflict of interest: None declared

Ethical approval: Not required

REFERENCES

1. Khan A, Shehmar M, Gupta J. Uterine fibroids: current perspectives. *Int J Womens Health.* 2014;6:95-114.
2. Lee HJ, Norwitz ER, Shaw J. Contemporary Management of Fibroids in Pregnancy. *Rev Obstet Gynecol.* 2010;3(1):20-27.
3. Donnez J, Donnez O, Dolmans MM. Safety of treatment of uterine fibroids with the selective progesterone receptor modulator, ulipristal acetate. *Expert Opinion Drug Safety.* 2016;1679-86.
4. Monleón J, Martínez-Varea A, Galliano D, Pellicer A. Successful pregnancy after treatment with ulipristal acetate for uterine fibroids. *Case Reports Obstet Gynecol.* 2014;2014.
5. Szamatowicz M, Kotarski J. Selective progesterone receptor modulator (ulipristal acetate--a new option in the pharmacological treatment of uterine fibroids in women. *Ginekol Pol.* 2013;84(3):219-22.
6. Lai J, Caughey AB, Qidwai GI. Neonatal outcomes in women with sonographically identified uterine leiomyomata. *J Matern Fetal Neonatal Med.* 2012;25:710-3.
7. Noor S, Fawwad A, Sultana R, Bashir R, Jalil H, Suleman N et al. Pregnancy with fibroids and its and its obstetric complication. *J Ayub Med Coll Abbottabad.* 2009;21:37-40.
8. Eze CU, Odumeru EA, Ochie K. Sonographic assessment of pregnancy co-existing with uterine leiomyoma in Owerri, Nigeria. *Afr Health Sci.* 2013;13:453-60.
9. Donnez J, Tatarchuk TF, Bouchard P, Puscasiu L, Zakharenko NF, Ivanova T et al. Ulipristal acetate versus placebo for fibroid treatment before surgery. *N Engl J Med.* 2012;366:409-20.
10. Donnez J, Tomaszewski J, Vazquez F, Bouchard P, Lemieszczuk B, Baro F et al. Ulipristal acetate versus leuprolide acetate for uterine fibroids. *N Engl J Med.* 2012;366:421-32.

Cite this article as: Kale AR. Ulipristal acetate (UPA) for fibroids–IVF outcomes following treatment with UPA after IVF failure: series of 2 case reports. *Int J Reprod Contracept Obstet Gynecol* 2017;6:3177-81.