

Post-IVF pregnancy in HCV-positive patient with uterine fibroids after treatment with ulipristal acetate

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ABSTRACT

An infertile HCV-positive woman with fibromatosis had several ART cycles without success. She underwent ulipristal acetate (UA) treatment after developing myomas. No hepatic alterations were reported and a significant reduction in the volume of the myomas was obtained. Subsequently she underwent transfer of a cryopreserved blastocyst and became pregnant, going on to give birth to a healthy baby. The present case of pregnancy, obtained after a 3-month therapy with UA without a subsequent myomectomy, demonstrates the positive effect that this drug may have in terms of fertility improvement and its safety in an HCV-positive patient with normal hepatic function.

KEYWORDS

Ulipristal acetate, myomas, HCV.

Introduction

Uterine fibroids are benign tumors of smooth muscle tissue and are the most common female neoplasms, affecting 30% of women of reproductive age ^[1,2].

Their diagnosis is easily performed by a pelvic ultrasonography (US), but their clinical presentation greatly depends on their size, number, and location ^[2,3]. In particular, the impact that myomas may have on reproductive potential is still under debate; voluminous intramural and submucosal fibroids seem to be associated with a reduced pregnancy rate, increased abortion rate ^[4-6], and with a higher risk of preterm delivery and fetal intrauterine death ^[7-10]. Their management, however, particularly in case with reproductive problems, is controversial.

Hysterectomy is well known to be the most effective long-term treatment, but this invasive approach is not suitable for patients seeking pregnancy, in whom other, less invasive, solutions should be considered first: myomectomy, for example, which can be performed via a mini-invasive approach ^[7]; microwave systems; uterine artery embolization or pre-surgical pharmacological options in pursuit of a less invasive surgery ^[4]. When choosing the most suitable approach to treat fibromatosis, especially in infertile patients, physicians must always take into account that surgical myomectomy carries potential risks (pelvic/intrauterine adhesions and loss of uterine continuity) [7] and that a medical treatment may be a valid alternative [4].

Among the available medical options, ulipristal acetate (UA) has grown in prominence over time. UA, a selective progesterone receptor modulator, is normally used in the attempt to reduce myoma volume before surgical interven-

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tion. Recent studies on UA have pointed out that this drug can achieve the same clinical results as gonadotropin-releasing hormone agonists, but its effects are longer lasting. For this reason, UA has become the drug of choice, particularly in *in vitro* fertilization (IVF) candidates ^[4,11,12], to optimize the chances of success with assisted reproduction technologies (ARTs) ^[12,13]. UA has been demonstrated to control the symptoms caused by fibroids, such as pelvic discomfort or pain and bleeding, to reduce their size by up to 30-40% in the space of few months and, especially, to maintain the myoma volume reduction at six months after treatment completion ^[3,4,12-14]. Its safety has been confirmed by the PEARL III and IV studies ^[14]. Increases in endometrial thickness caused by UA are considered reversible pharmacodynamic responses ^[2,4,15] and no adverse effects on pregnancy or the fetus have been reported either ^[14,16,17]. Therefore, this new pharmacological approach is today considered an effective non-invasive alternative to surgery to optimize the chances of IVF ^[12,13].

The primary route of excretion of UA is the liver, with a mean value of 73% of the administered dose recovered in feces. The second route is renal excretion, with a mean of 6% of the administered dose recovered in urine ^[18]. This

clarification serves to explain why, today, UA is under the spotlight for its safety limits. Since authorization of the drug in 2012, eight cases of serious liver injury, including cases of hepatic failure needing liver transplantation, have been reported worldwide in women using UA for uterine fibroids. Subsequently, from May 2018, the European Medicines Agency (EMA) recommended several measures to minimize the risk of rare liver complications with UA, including liver function monitoring in current and recent users^[18]. More recently, a new warning has been issued by the European Commission following the report, in February 2020, of a new clinical case of severe hepatic injury related to the use of UA^[19]. On 12 March 2020, the EMA's safety committee (PRAC) recommended that women stop taking 5-mg UA for uterine fibroids while a safety review is ongoing.

Literature concerning the effects of UA on pregnancy probabilities in patients with myomas is still in its early stages; the few existing retrospective studies and case reports on the subject demonstrate that UA may positively affect the pregnancy rate, with all pregnancies occurring only 3 months after the end of treatment^[17] and no significant fibroid regrowth occurring during gestation^[2,17], even when used alone without a subsequent surgical intervention.

The present case report aims to underline the safe and effective profile of UA in the treatment of uterine fibroids, particularly in the context of efforts to improve the woman's fertility potential and to increase the chances of pregnancy in infertile patients.

Case description

Our patient was 33 years old when she first entered the Humanitas Fertility Center in 2012 because of a history of primary infertility. She and her husband had been trying to conceive since 2009. She was HCV positive, with a chronic infection known since 2003, but was not under treatment, showing no enzymatic abnormalities and no signs of active liver damage. Her past and present medical history was otherwise silent. Her gynecological anamnesis and physical examination were negative; US examination showed a mildly inhomogeneous myometrium, a good endometrial appearance and multi-follicular ovaries. Her hystero-salpingography was negative, while her hormonal levels showed a situation of only mildly reduced ovarian reserve with the following hormone levels: FSH 8.30 mUI/mL, LH 3.70 mUI/mL, and AMH 1.20 ng/mL.

In view of the idiopathic female infertility problem and the finding of seminal fluid good enough for spontaneous conception, the couple was referred to a program of *in vivo* assisted reproduction. Between 2012 and 2013, five consecutive intrauterine inseminations were performed, all with negative outcome. Because of the failure of the intrauterine inseminations, in 2013 the couple started cycles of IVF. Over the following years, i.e. 2013-2015, the couple underwent 4 IVF cycles; the first 3 all ended with no cryopreserved embryos and no successful implants, while, after the last one, one blastocyst was successfully stored.

In February 2015, the woman started the preparation for the transfer of the cryopreserved embryo. A new transvaginal US showed, for the first time, multiple leiomyomas, 2 posterior intramural fibroids measuring 44.7 x 34.7 x 45.0 mm and 34.0 x 26.6 x 36.0 mm, respectively, a posterior one measuring 51.0 x 43.0 x 53.0 mm in the fundus of the uterus, and an anterior sub-serous one with a size of 15.0 x 14.0 x 14.0 mm. The endometrium was linear and seemed not to be affected by the fibroids.

Although the patient was treated before the EMA alert, we decided to control her monthly liver enzymes, according to the prescription of the hepatologist.

A 3-month-long therapy with UA (Esmya, 5 mg, Gedeon Richter, Hungary) at 5 mg per day was prescribed to the patient starting on February 17th 2016; at the end of the treatment, on May 17th 2016, a new US showed marked shrinkage of the myomas with the biggest one measuring 34.0 x 33.0 x 32.0 mm. In June 2016, a second diagnostic hysteroscopy was performed to confirm the regularity of the uterine cavity prior to embryo transfer. Since the examination showed no anatomical abnormalities and the endometrial biopsy was negative, on June 17th 2016, the woman underwent embryo transfer of the cryopreserved blastocyst. Two weeks later, her beta hCG levels were positive and thereafter continued to rise normally.

The pregnancy evolved uneventfully, and the patient gave birth at term by emergency cesarean section for chorioamnionitis to a healthy baby weighing 3300 g.

Conclusions

The updated literature dealing with UA in the treatment of leiomyomas is still in its early stages and, to date, few case reports and retrospective studies on this topic have been published. This case report is therefore intended to enrich present knowledge by raising some interesting points for further research.

First of all, this case provides some clues about the safety of UA in the treatment of leiomyomas in patients seeking pregnancy; the use of UA, for a cycle of 3 months at a dose of 5 mg per day, indeed showed no negative effects on the ovarian reserve. The parameters used at our center for the evaluation of ovarian reserve (AFC, AMH, FSH) showed no significant alterations in our patient before or after the 3-month-long therapy with UA.

Furthermore, this case also demonstrates how UA, even if used alone without any subsequent surgical myomectomy, may on its own improve the chances of pregnancy; soon after the end of the treatment with UA, our patient had the cryopreserved blastocyst transferred and successfully became pregnant.

Finally, our case report also showed UA to be safe from the hepatological point of view. In fact, the patient was known to be HCV positive and the hepatologist's approval was obtained for before beginning the UA cycle. The patient received the therapy for the entire 3-month-long period with the placet of the hepatologist and, both during and after the

therapy, no alterations in her liver enzymatic profile were reported. Of course, a single case report cannot serve as a basis for stating that UA is proven to be a safe treatment in HCV-positive patients and further information and updated recommendations are therefore still necessary. This is the reason why an answer from PRAC, once the ongoing review is concluded, will play a leading role in our clinical practice.

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