Management of Fibroids Prior to in Vitro Fertilization. Case Reports

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Research Article

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Abstract

BACKGROUND. Uterine fibroids are common benign uterine neoplasms in women in reproductive age and pregnancy desire. Several surgical approaches for symptomatic fibroids are available, such as surgical or pharmacologic treatments. We report three cases of fibroids treatment in women with primary sterility.

CASE PRESENTATION. The first case of a successful in vitro fertilization (IVF) after ulipristal acetate (UPA) as an alternative treatment to reduce the fibroids size in a patient with two previous abdominal myomectomies, resulting in an evolutive pregnancy. The second patient underwent several myomectomies (both abdominal and hysteroscopic) in a long period of time. And the third one of a successful IVF after UPA in a patient with a submucous fibroid which induced myoma migration leading to its prolapse.

CONCLUSIONS. Myomectomy appears to be the gold standard treatment for fibroids in women with reproductive desires. Nevertheless, more series are essential for establishing the safety of UPA as a treatment of symptomatic fibroids prior to pregnancy.

Background

Submucous and intramural fibroids may be associated with infertility and increased miscarriage rate. The management of fibroids in women with reproductive desires remains controversial [1]. The decision of treatment and how to treat them must be influenced by factors as reproductive desires or women´s desire of uterus preservation. Several surgical approaches and pharmacologic treatments for symptomatic fibroids have been proposed [2].

Case Presentation

Case I

A 37-year-old nulliparous woman suffering from symptomatic uterine fibroids causing menorrhagia, dysmenorrhea and increased urinary frequency was referred to our center to assess IVF. She had had two abdominal myomectomies 4 and 7 years before, with removal of two and three fibroids respectively. Pregnancy was being searched for 6 years.

Ultrasound scan (US) and magnetic resonance image (MRI) revealed myomatous uterus describing several fibroids: extrapelvic subserous intramural in fundus (sized 83x70x69 mm) subserous along the left border, reaching cervix (sized 75x64x42 mm), anterior subserous fibroid that imprints on the bladder (sized 73x51 mm) among other smaller fibroids (Fig. 1).

Hysteroscopy findings were: uterine cavity with a proliferative endometrium, with a small relief in the posterior contour, in probably relation with a myoma. Antimullerian hormone and antral follicle count revealed a diminished ovarian reserve. Male studies were normal.

Medical treatment with a 12-week course of 5 mg a day of UPA was offered prior to IVF, assessing the risk of hysterectomy if she underwent a new myomectomy. During the treatment she noticed improvement in her symptoms, with reduction of the uterine bleeding in the first week of treatment. As it can be observed in Fig. 2, MRI prior and after UPA treatment revealed a 35% fibroid volume reduction of the one in fundus and 40% reduction of the anterior subserous myoma.

IVF was performed when an unaffected uterine cavity and size reduction of myomas were achieved. Antagonist protocol for controlled ovarian stimulation (COS) was carried out with 150 international units (IU) a day of biosimilar follicular stimulating hormone (FSH) and 125 IU a day of human menotropin hormone (HMG) for 11 days; cetrorelix for 6 days starting on the 6th day. Final oocyte maturation and ovulation trigger shot was performed with 250 μg of human chorionic gonadotropin (hCG) and four oocytes were retrieved. Three oocytes were fertilized and two embryos were obtained. Single evolutive pregnancy was achieved after transfer of vitrified-thawed embryos on day 3.

The patient had a threatened miscarriage during the 7th week of pregnancy, but the pregnancy carried on and delivery took place by caesarean section due to cervical fibroid at 37 weeks. A healthy male infant weighing 2840 g was delivered.

Case II

A 30-year-old woman with history of uterine fibroids and 2 years of primary sterility. She had underwent an abdominal myomectomy two years before and a hysteroscopic morcellation one year before. US revealed a polymomatous uterus, with a submucous fibroid (sized 52 mm) on the right border, and a posterior subserous intramural fibroid (sized 48 mm) (Fig. 3). Hysteroscopic study revealed a posterior FIGO type 3 submucous fibroid (sized 30 mm) that protruded 10% in the cavity, not candidate for morcellation or hysteroscopic resection (Fig. 4). A 12-weeks course of UPA treatment was offered but the patient refused. During the next year she had two spontaneous miscarriages. No changes were observed in a new US and hysteroscopy. A new abdominal myomectomy without opening the endometrial cavity was performed. Four months after surgery, the US revealed an anterior submucous fibroid (sized 16 mm). A new hysteroscopic morcellation was performed and IVF was offered but she became pregnant spontaneously three months later. The patient is 32 weeks pregnant at this moment.

Case III

Couple referred 2 years of primary sterility. Male seminogram revealed 98% of teratozoospermia. US of the woman, aged 35, found out a posterior intramural fibroid close to the uterine cavity. The size of the myoma was 39 mm (Fig. 5). Hysteroscopic study was normal. The patient had a spontaneous miscarriage just before performing IVF. Two months later IVF was performed. COS was carried out with an antagonist protocol with 150 IU a day of recombinant FSH (rFSH) for 10 days and cetrorelix for 5 days starting on the 6th day. Final oocyte maturation and ovulation trigger shot was performed with 250 μg of hCG. 12 oocytes were retrieved. Fertilized was accomplished in 10 of them. Single embryo transfer of a fresh embryo in day 3 was performed without achieving pregnancy. Three embryos were vitrified. Two months later, it was suspected a degeneration of the fibroid previously described during a US. The

myoma had grown, with a new size of 46 mm and distorted the uterine cavity. A new hysteroscopic was performed and a type 1 fibroid on the posterior surface was described. Medical treatment with a 12-week course of UPA previous to hysteroscopic morcellation was prescribed. After two months of treatment the patient came to the emergency room due to vaginal bleeding. The gynecological examination revealed a prolapsed fibroid that required an emergency vaginal surgery to remove it. Pregnancy was finally achieved after vitrified-thawed embryo transfer. A healthy male infant was delivered at 41 weeks of pregnancy, weighing 3740 g.

Discussion

There are several medical and surgical treatments for patients with symptomatic uterine fibroids and pregnancy desire. Choosing the most optimal therapy in each case is sometimes controversial [1]. Myomectomy may improve fertility outcomes in women with submucous and intramural fibroids [1]. Nevertheless, there is still insufficient evidence from randomised controlled trials to establish the effect of myomectomy to improve fertility [1, 3].

Alternative medical treatment with UPA causes decrease of excessive menstrual bleeding and reduced total fibroid volume [4]. UPA was not inferior to LPA in terms of menstrual bleeding control in women with symptomatic fibroids before surgery [5]. It has been reported that repeated 12-week courses of 5 mg a day of UPA is effective and safe for bleeding and pain control, fibroid volume reduction, and restoration of quality of life in patients with symptomatic fibroids [1, 6]. UPA has also shown fibroid size reduction and can induce myoma migration, leading to the normalization of the uterine cavity in patients with previous distortion due to submucous fibroids [6]. In these cases, medical management could replace surgery. The optimal moment to conception following a treatment course with UPA is not clear [7]. Decreased endometrial receptivity due to PAECs should be considered [7, 8] although it is a reversible pharmacological response and it has been reported that endometrium returns to normal spontaneously after finishing UPA [5].

In a systematic review of Gasperis et al [7], a total of 71 pregnancies were followed after UPA treatment. 39% patients achieved 27 (38%) pregnancies following UPA treatment without interval myomectomies. The majority of pregnancies occurred more than 3 months after finishing UPA treatment course. 10 patients conceived within 3 months of stopping treatment, achieving 70% of live births.

In the available bibliography four cases of IVF were performed after UPA treatment and two pregnancies ended in a live birth [9, 10]. Embryo transfer was performed three months after finishing UPA therapy in both cases. Spontaneous first trimester abortion ocurred in the other two [7].

Khaw et al [11], in a recent systematic review compared pregnancy outcomes after fertility-preserving treatment of uterine fibroids. They analyzed live birth and miscarriage rates after four treatment modalities: UPA therapy, myomectomy surgery and radiological approach with uterine artery embolization (UAE) or thermal ablation. It is important to consider that results after UPA therapy were not included in the statistical analysis due to the limited number of cases. They conclude that myomectomy appears to

be, so far, the mainstay fertility preservation treatment for fibroids and seems to have better pregnancy outcomes compared to UPA, UAE or ablation theraphy [10]. However, myomectomy has specific surgical risks including pelvic or intrauterine adhesions depending on the surgical approach [12]. The risk of hysterectomy has to be taken into account in women without reproductive wishes fulfilled. The rates of appearance of new myomas after five and eight years after myomectomy have been established in 53 and 84 percent respectively [13]. There is also a remarkable percentage of patients, around 15–20% [14] (both in laparoscopy and in laparotomy access) with an incomplete resection of all of the fibroids.

To improve fertility outcomes in advance-age patients, Orvieto et al [15] propose ovarian stimulating cycle, aiming the embryo cryopreservation [16], followed by myomectomy or 12 weeks course of UPA treatment.

Submucosal fibroids have a detrimental impact on the chances of success with IVF [17] and it is recommended to treat them in sterile patients. Regardless of the treatment applied, the proven restoration of uterine cavity maximizes the chances of a successful IVF [12]. Expectant management in asymptomatic subserous fibroids is also accepted. However, the management of noncavity-distorting intramural fibroids prior to IVF/ICSI is under debate. Their presence could hinder pregnancy and the vascularization distortion caused by surgery could provoke negative effects in subsequent pregnancies. Current evidence suggests a detrimental impact of the presence of these fibroids [17].

On the other hand, there is a large bibliography available about IVF after myomectomy. The cumulative incidence of clinical pregnancy improves significantly after myomectomy in women undergoing IVF [18].

Further studies are needed to clarify the role of UPA in IVF, which patients could be suitable and what real percentage could avoid ending up in a surgical procedures [12]. However, this can be hampered because in 2018, European Medicines Agency (EMA) has informed rare but serious cases of liver injury during UPA treatment. They recommended liver monitoring to minimize this risk. Recently, on 12 March 2020, EMA's safety committee (PRAC), recommended to stop all UPA treatments for uterine fibroids until its benefit-risk ratio is reevaluated, motivated by the appearance of a new case of severe liver failure.

Conclusions

In conclusion, myomectomy appears to be the gold standard treatment for women wishing conservative management of fibroids looking for a subsequent pregnancy [11]. More series are essential for establishing the safety of UPA as a treatment of symptomatic fibroids prior to pregnancy. No pregnancy-related complications or teratogenic effects have been reported to date, so as UPA is the only medical treatment available for fibroids, we think it should be considered before offering surgery in those patients at high surgical risk.

Abbreviations

COS: controlled ovarian stimulation

EMA: European Medicines Agency

FSH: follicular stimulating hormone

hCG: human chorionic gonadotropin

HMG: human menotropin hormone

IU: international units

IVF: in vitro fertilization

MRI: magnetic resonance image

rFSH: recombinant FSH

UAE: uterine artery embolization

UPA: ulipristal acetate

US: Ultrasound scan

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Written informed consent was obtained from all patients.

Availability of data and material

The datasets used and/or analyzed during the current study are available.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

TGH, MCU, ICG, MVL and ICG contributed to patients' healthcare and the collection of the data. TGH and VGG contributed to write the manuscript. All authors contributed to revising the manuscript, and approved the final version.

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Figures

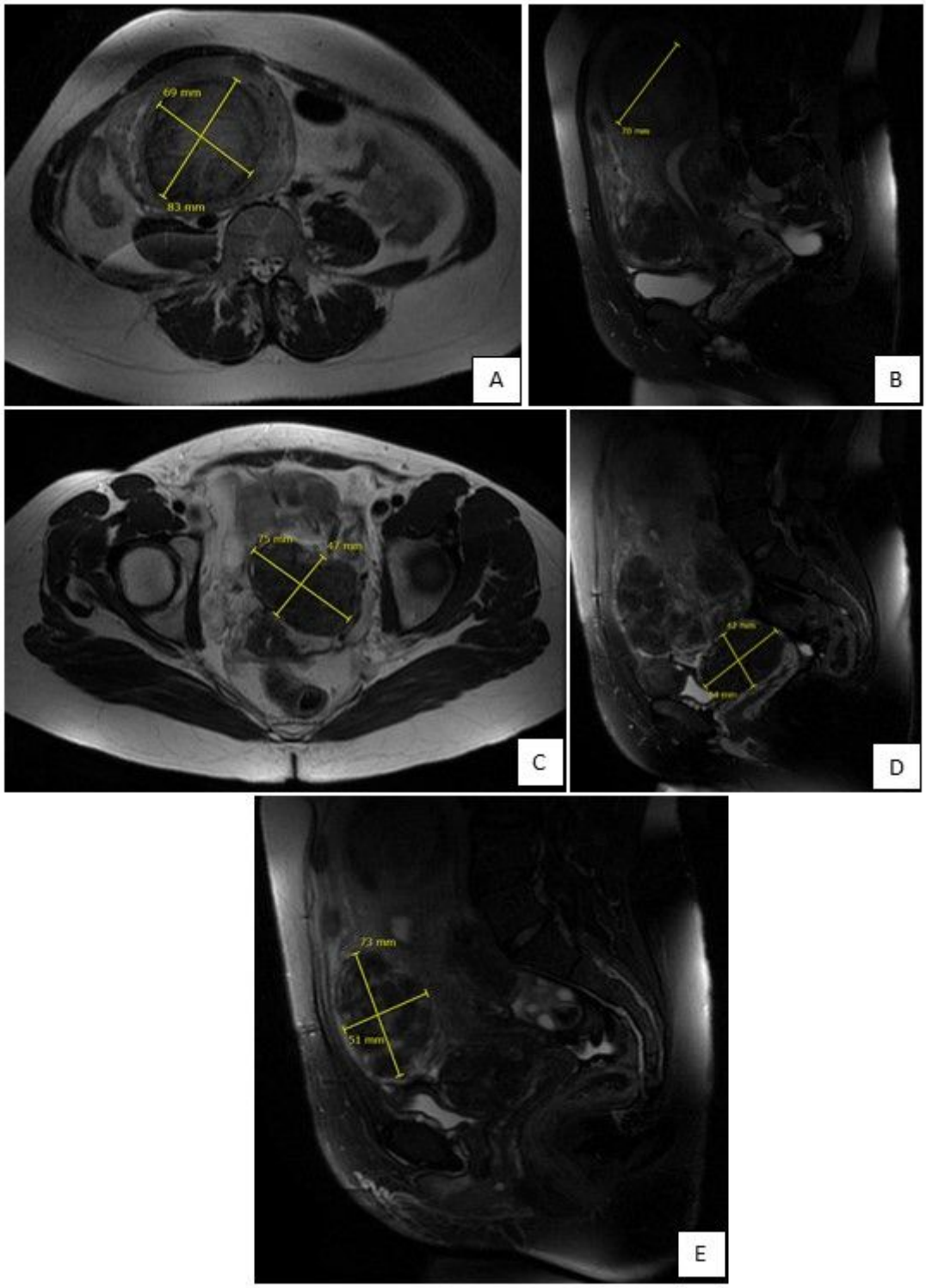

Figure 1

T2-weighted RMI previous to UPA treatment. Cross-section (A) and Sagittal-section (B) of extrapelvic subserous intramural fibroid in fundus. Cross-section (C) and Sagittal-section (D) of subserous fibroid along the left border, reaching cervix. Sagittal-section (E) of anterior subserous fibroid that imprints on the bladder.

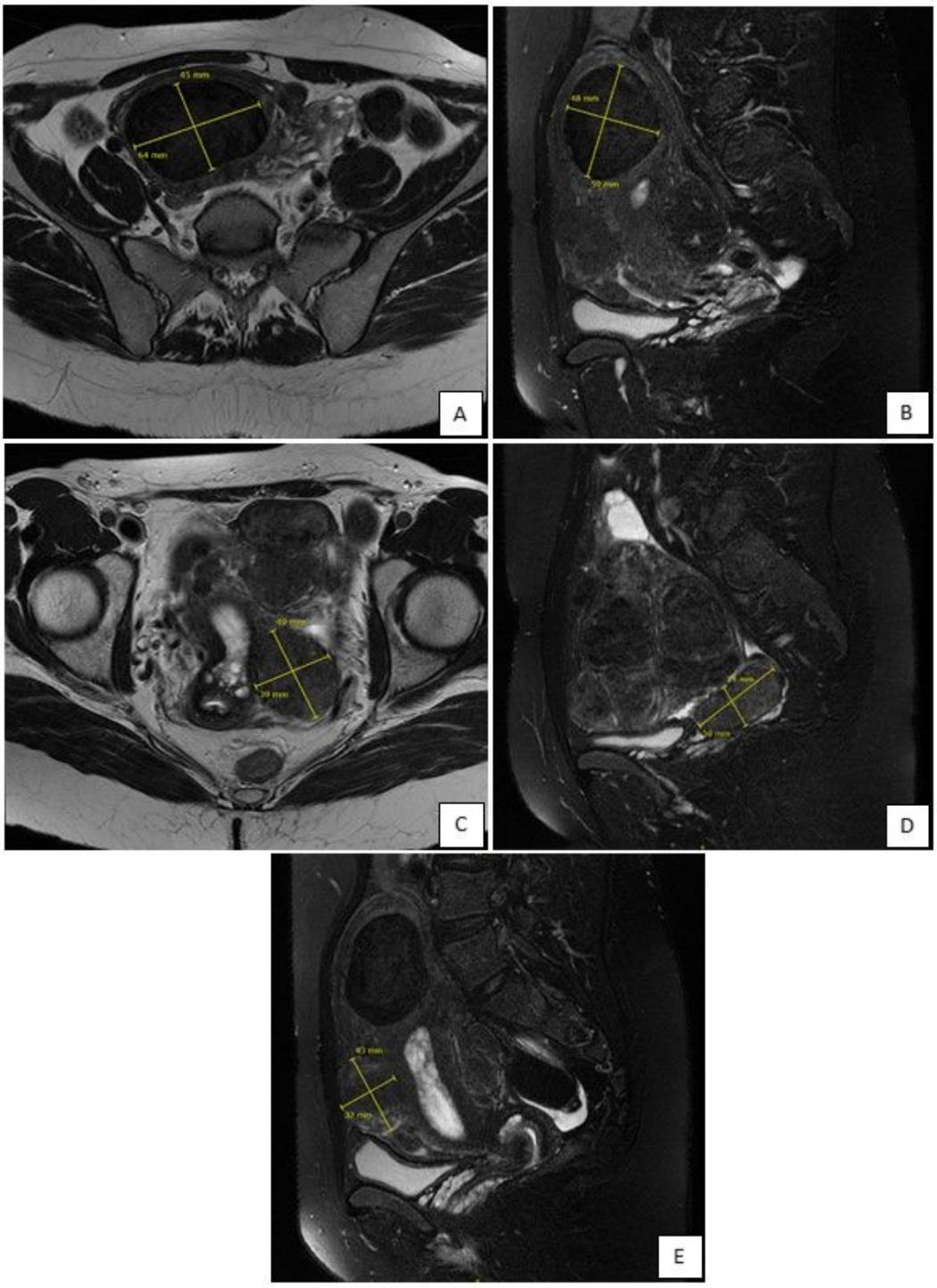

Figure 2

T2-weighted RMI after UPA treatment. Cross-section (A) and Sagittal-section (B) of extrapelvic subserous intramural fibroid in fundus after UPA treatment. Cross-section (C) and Sagittal-section (D) of subserous fibroid along the left border, reaching cervix. Sagittal-section (E) of anterior subserous fibroid that imprints on the bladder

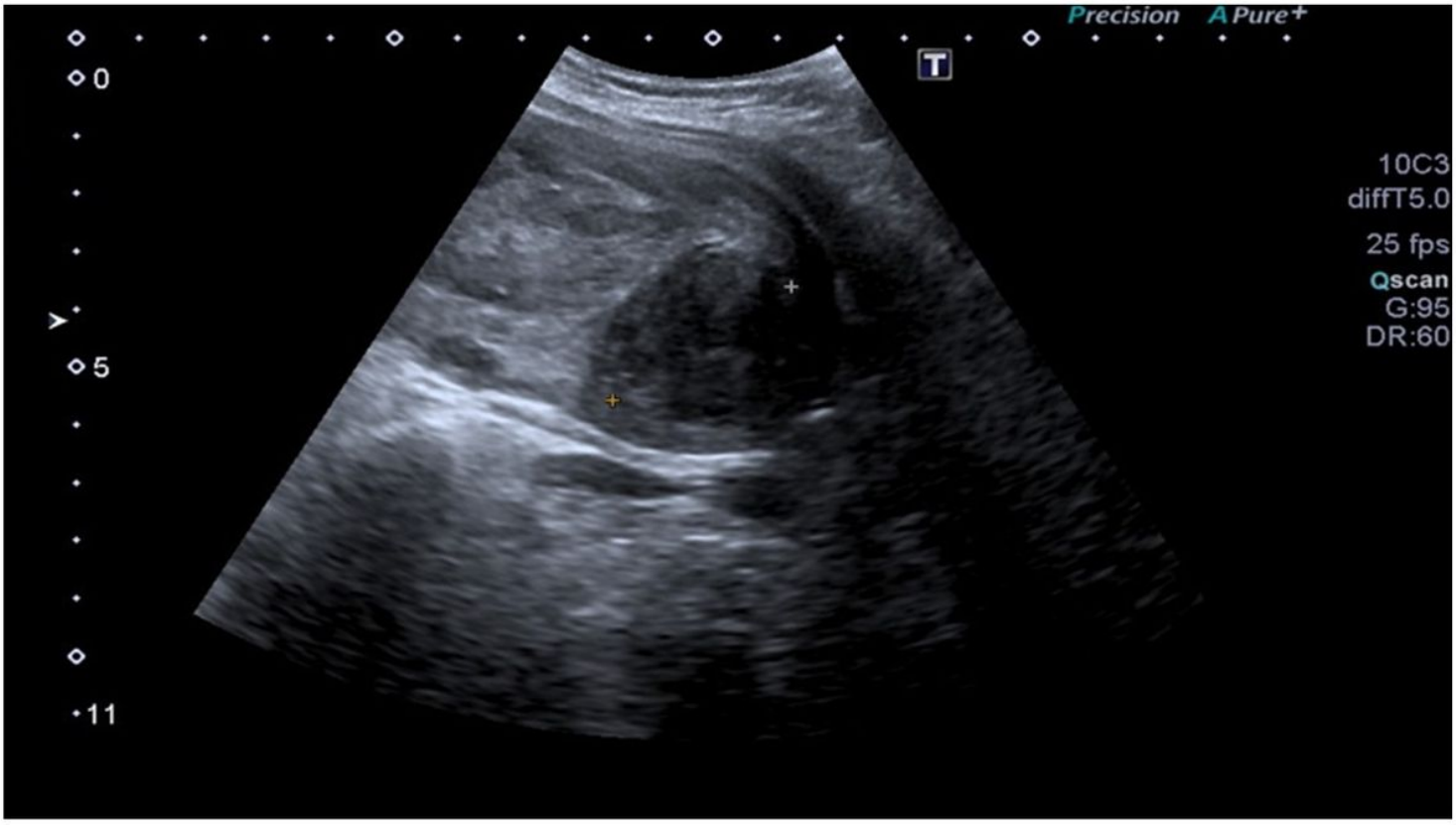

Figure 3

US. Posterior subserous intramural fibroid.

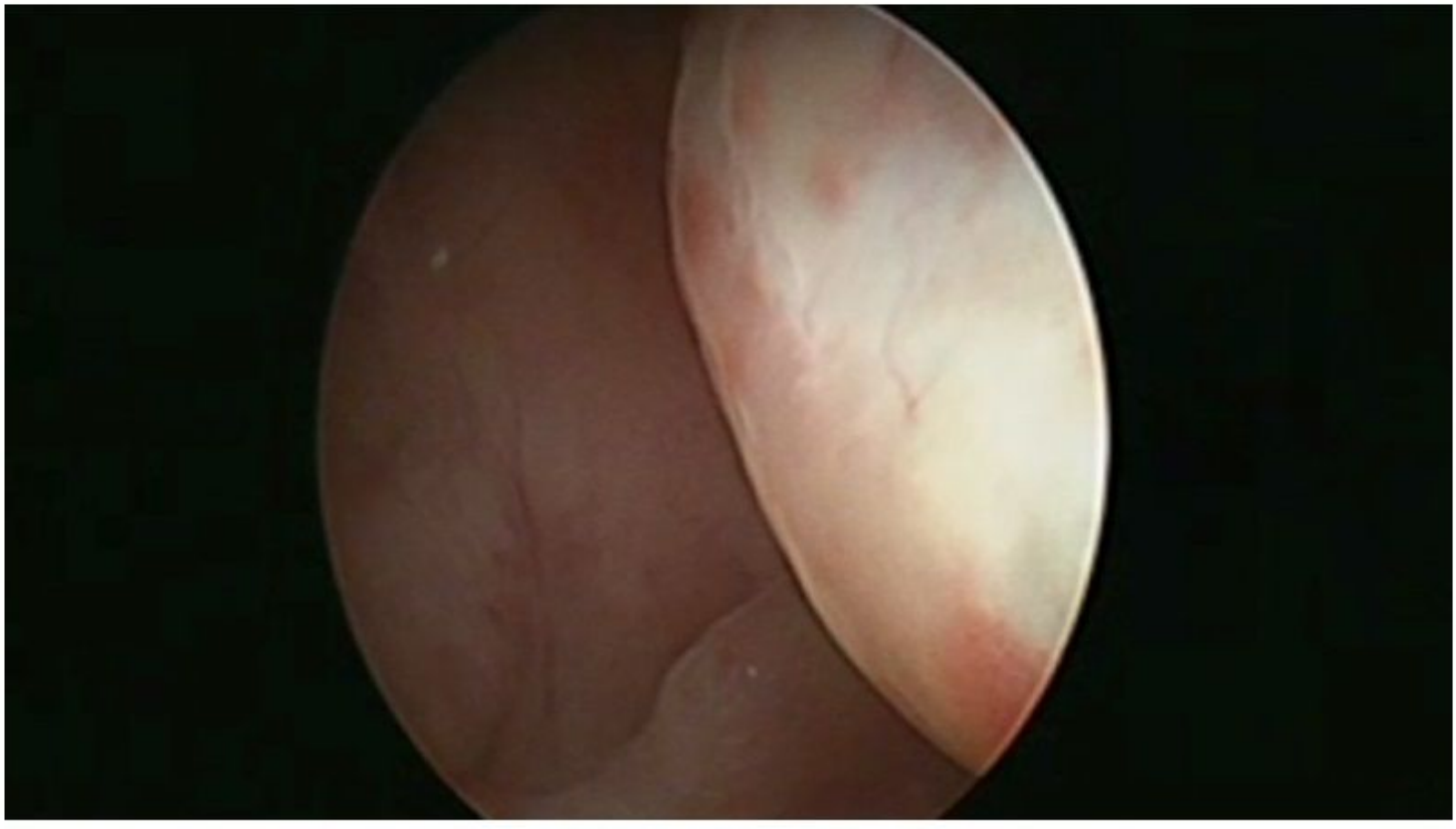

Figure 4

Hysteroscopy image of the posterior submucous fibroid protruding into the uterine cavity.

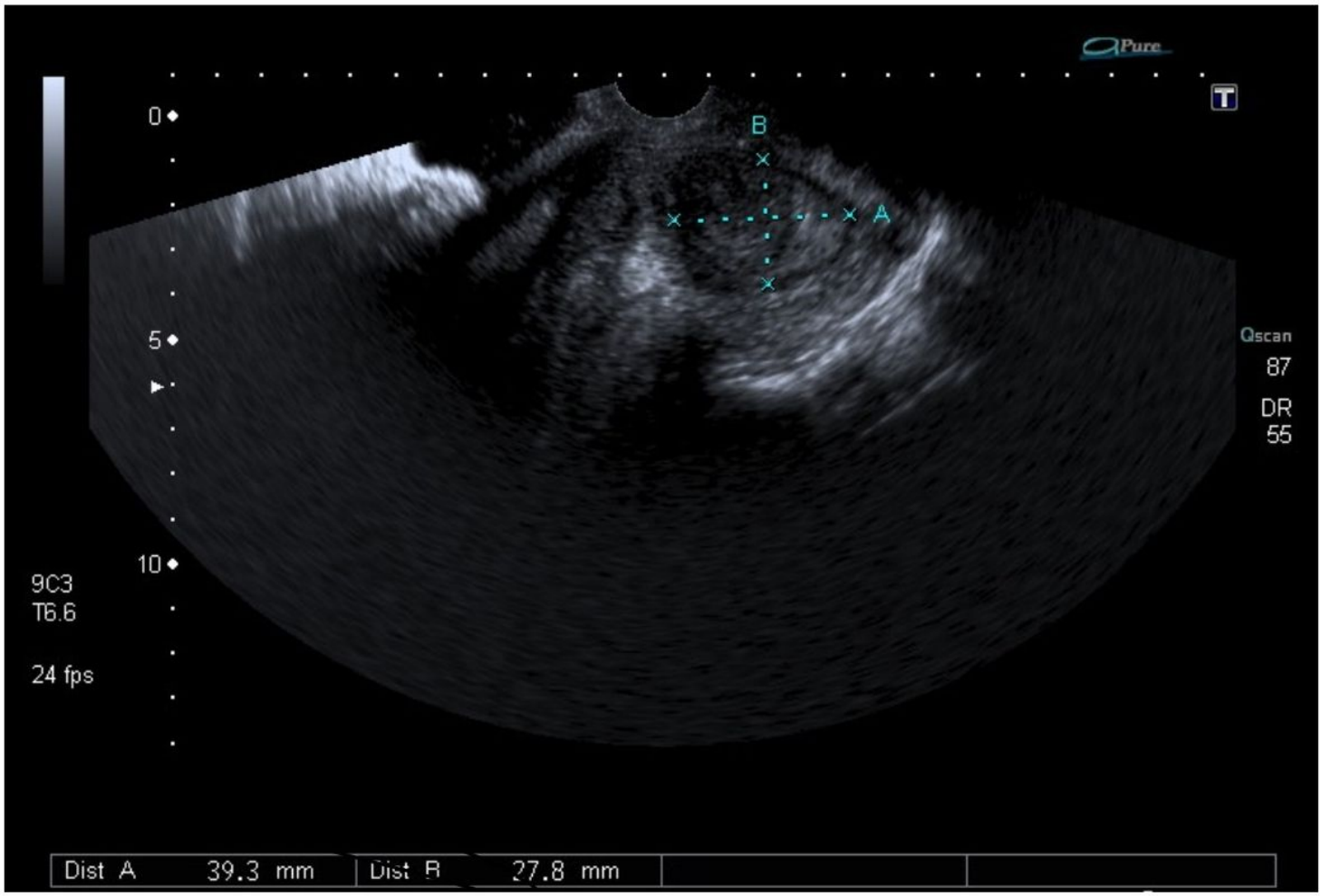

Figure 5

Posterior intramural fibroid of 39mm of diameter, close to the uterine cavity.

Supplementary Files

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- CAREGUIDELINES.pdf