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A 40-Year-Old Woman with Inoperable Uterine Fibroids Treated with Combined Uterine Artery Embolization and Relugolix

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Patient: Female, 40-year-old
Final Diagnosis: Fibroids
Symptoms: Menometrorrhagia
Clinical Procedure: Medical treatment • surgery
Specialty: Obstetrics and Gynecology

Objective: Unusual clinical course
Background: Surgery was once considered the only possible treatment for uterine fibroids. However, a more conservative treatment approach can preserve women's reproductive capacity. In recent years, uterine artery embolization (UAE) and medical treatments have been introduced as a minimally or non-invasive therapeutic option. Relugolix is a non-peptide gonadotrophin-releasing hormone (GnRH) receptor antagonist used to reduce the release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH). This report presents the case of a 40-year-old woman with inoperable uterine fibroids managed with combined uterine artery embolization and Relugolix, a non-peptide gonadotrophin-releasing hormone (GnRH) receptor antagonist.
Case Report: A woman in her 40s presented with recurrent menometrorrhagia and an 80-mm uterine fibroid causing bleeding and anemia. Due to her medical history and previous surgeries, surgery was deemed risky. Instead, a conservative approach involving UAE followed by Relugolix combination therapy (Relugolix-CT) was pursued before performing minimally invasive surgery. Following bilateral UAE, the ultrasound scan showed there had already been a reduction in the fibroid size. Right after the UAE, the patient was discharged with Relugolix-CT, which reduced the symptoms and helped further reduce the fibroid's size and vascularity. Six months later, a mini-resectoscopic myomectomy was performed under local anaesthesia.
Conclusions: This case underscores the effectiveness of UAE and Relugolix-CT as a pre-surgical strategy for large uterine fibroids in patients who are not immediately suitable candidates for major surgery. This new combined approach can lead to improved patient outcomes and reduced surgical risks.
Keywords: Menopause • Women • Women's Health

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Introduction

Uterine fibroids are benign uterine tumors that affect 20-80% of women by age 50, with higher prevalence and severity in African American women [1]. The diagnosis is based on symptoms: heavy menstrual bleeding, pelvic pain, bulk symptoms, or infertility; and imaging: transvaginal ultrasound (first line), magnetic resonance imaging for detailed evaluation, and hysteroscopy for the cavity assessment [1]. Their management relies on observation (especially for asymptomatic or near-menopausal women; medical therapy: hormonal treatments (eg, GnRH agonists, oral contraceptives) and tranexamic acid for bleeding control; minimally invasive surgeries like uterine artery embolization, and MRI-guided focused ultrasound and surgery including myomectomy for fertility preservation or hysterectomy for definitive treatment [1,2]. Management of fibroids is tailored based on symptoms, fertility goals, and patient preferences [1,2].

Surgery was once considered the only possible treatment for uterine fibroids [2]. However, a more conservative treatment approach can preserve women's reproductive capacity [2]. In recent years, uterine artery embolization (UAE) has been introduced as a minimally invasive therapeutic option for symptomatic uterine fibroids, with a low reported complication rate in the literature [1,2]. This procedure was first reported in 1995 by Ravina et al [3].

In a 2008 practice bulletin, the American College of Obstetrics and Gynecology (ACOG) concluded, with level A evidence, that based on long- and short-term outcomes, UAE is a safe and effective therapy [4]. This technique is now a well-established minimally invasive therapy, with strong evidence supporting its safety and efficacy [4].

Generally, most symptomatic patients who could be candidates for surgical treatment are also candidates for UAE [5]. Absolute contraindications for UAE include viable pregnancy, active infection, and suspected uterine, cervical, or adnexal malignancy [5]. Relative contraindications, which require appropriate management, include contrast agent allergy, renal impairment, and

coagulopathy [5]. Another relative contraindication is large fibroids (>10 cm) [5]. However, in recent years, some authors have demonstrated the safety and efficacy of the percutaneous procedure in these patients [5,6]. Additionally, the presence of pedunculated subserosal fibroids, particularly those with an attachment of less than 50% of the diameter, is also considered a relative contraindication [5,6].

The feasibility assessment of UAE must be carried out by the interventional radiologist in full collaboration with the gynecologist [7]. They should discuss the available therapeutic options

(medical or surgical) with the patient [7-9]. Indeed, it is important to consider that therapy must be individualized considering the patient's age, symptoms, comorbidities, and number and characteristics of uterine fibroids [10]. Therefore, a radiological consultation before UAE is crucial to determine the patient's preference regarding uterine-sparing therapy, prior fibroid therapies, or desire for future pregnancy [7,8]. Moreover, it is important to analyze recent fibroid imaging before proceeding with UAE [7-10].

It has been shown that contrast-enhanced magnetic resonance imaging (MRI) is more accurate than pelvic ultrasound (US) for characterizing uterine fibroids [7-9]. MRI allows not only an assessment of the pelvis and vascular structures but also an evaluation of fibroid location, enhancement characteristics, and other uterine pathologies that can mimic fibroid symptoms, such as adenomyosis or malignancy [7].

Recent research indicates that performing UAE to de-vascularize leiomyomas before laparoscopic or hysteroscopic myomectomy may be a feasible technique for a multidisciplinary approach for large uterine myomas, allowing minimally invasive surgery [8,9].

Relugolix is an oral gonadotropin-releasing hormone (GnRH) receptor antagonist that rapidly suppresses pituitary gonadotropin secretion, leading to reduced levels of estrogen and progesterone [10]. This mechanism is particularly useful in managing hormone-dependent conditions like uterine fibroids, which are driven by estrogen and progesterone [10].

Unlike GnRH agonists, which initially cause a hormone flare before suppression, Relugolix offers rapid suppression without the flare, making it a convenient and effective option [10].

Relugolix has been studied extensively for its ability to reduce symptoms of uterine fibroids, particularly heavy menstrual bleeding [10]. A landmark study, Treatment of Uterine Fibroid Symptoms with Relugolix Combination Therapy, published in the New England Journal of Medicine by Al-Hendy et al (2021), evaluated its efficacy and safety especially in its combination Therapy: Relugolix was combined with estradiol (1 mg) and norethindrone acetate (0.5 mg) to mitigate hypoestrogenic adverse effects like bone loss and vasomotor symptoms [10].

Here, we present a case of a bulky uterine fibroid successfully treated with a personalized approach that included uterine artery embolization followed by with medical treatment with Relugolix combination therapy (Relugolix-CT) with 40-mg tablets of Relugolix plus 1 mg estradiol and 0.5 mg norethisterone acetate. After volumetric reduction and migration toward the endometrial cavity, a mini-resectoscopes myomectomy was performed under local anaesthesia.

We present the case of a case of a 40-year-old woman with inoperable uterine fibroids managed with combined uterine artery embolization and Relugolix, a non-peptide gonadotrophin-releasing hormone (GnRH) receptor antagonist, prior to surgery.

Case Report

A woman in her 40s with a history of recurrent menorrhagia was seen at our Gynecology Department during the summer of 2022. She had recurrent menorrhagia with secondary anemia that was resistant to conventional medical treatment for 6 years. She had no risk factors for taking estrogen-progestins. Transvaginal ultrasound revealed an 80-mm bulky uterine fibroid (Figure 1).

In her medical history, she had undergone 3 bowel surgeries due to gunshot wounds 6, 5, and 4 years before, and had 2 vaginal deliveries 9 and 7 years before. She had no other medical conditions nor alcohol or smoking habits. During her admission, she underwent an MRI, which confirmed the presence of an enlarged uterus caused by an 85.2×79.2 mm intramural formation with well-defined margins (Figure 2).

This formation was mainly vascularized from hypertrophic branches of the right uterine artery, while some hypertrophic branches of the left uterine artery vascularized its more peripheral components. After additional assessments (negative lactate dehydrogenase levels) and thorough counselling on various potential treatment approaches, including surgery with a high risk of intestinal injury, she opted for conservative management. Shortly after the MRI, a uterine artery embolization was scheduled.

One month later, bilateral uterine artery embolization was performed. A selective study of the hypogastric arteries was conducted, followed by super-selective bilateral catheterization of the uterine arteries using a microcatheter. Subsequently, embolization of the afferent branches to the identified uterine myoma was carried out (Hydropearl microspheres, 4 vials of 2 ml 600 microns

and 5 vials of 2 ml 800 microns). A favourable outcome was achieved during the final angiographic assessment, with no intraoperative complications. During the in-hospital follow-up period, which lasted 14 days, the patient experienced significant post-procedural pain, which was managed with morphine.

The day after the embolization, a transvaginal ultrasonography revealed a slight reduction in the size of the known leiomyoma (with a maximum diameter of 70 mm). Ten days following the embolization, a second transvaginal ultrasonography was conducted, showing no change in the fibroid dimensions

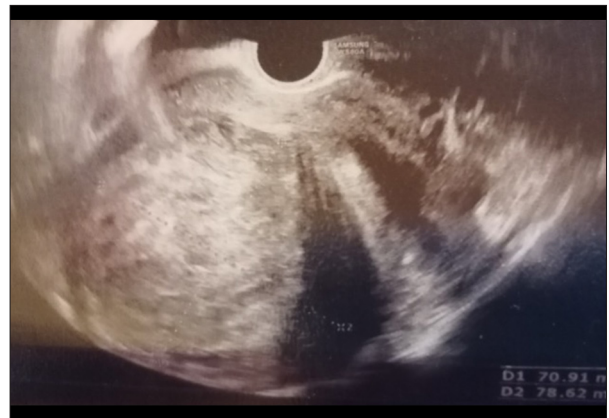


Figure 1. Ultrasound image before embolization, showing a bulky uterine fibroid (78.6×70.9 mm).

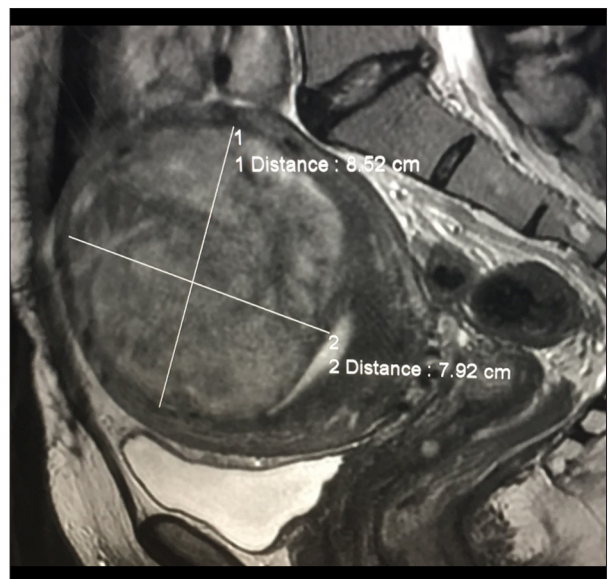


Figure 2. Pre-embolization magnetic resonance imaging (MRI) showing an intramural uterine fibroid (85.2×79.2 mm).

despite reduced vascularity. The patient was discharged with Relugolix-CT, one daily tablet for 12 weeks. Four months later, a gynecological examination was performed. The patient had a significant reduction in blood loss after the procedure and during medical therapy, with a return to normal hemoglobin levels. A transvaginal ultrasound revealed a 30-mm fundic intramural-submucosal myoma classified as FIGO 2-3. A subsequent MRI confirmed the presence of a FIGO 2 submucosal myoma with a notable reduction in size and vascularity (Figure 3).

Consequently, 10 days later, an outpatient mini-resectoscopic myomectomy (GUBBINI system, Tontarra Medizintechnik, Tuttlingen, Germany) was scheduled and carried out at the end of 2022 on local anaesthesia with the insertion of a 52-mg Levonorgestrel intrauterine system (LNG-IUS) (Benilexa – Gedeon Richter) for prophylactic therapeutic purposes.

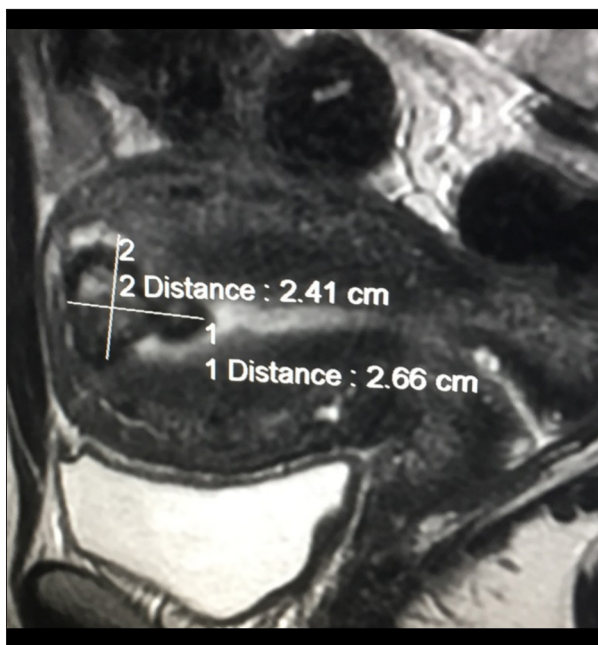


Figure 3. Magnetic resonance imaging (MRI) after embolization control showing a 26.6×24.1 mm fibroid.

Discussion

This case report demonstrates the successful use of combined uterine artery embolization (UAE) and Relugolix combination therapy (Relugolix-CT) to manage a large uterine fibroid in a high-risk surgical patient. The approach enabled significant fibroid reduction, symptom relief, and a minimally invasive myomectomy while preserving reproductive potential. It highlights an innovative, patient-centered strategy for managing complex fibroid cases.

Our patient presented with a large uterine fibroid causing debilitating symptoms such as metrorrhagia and pelvic pain. Considering the patient's history of previous surgical interventions and ostomies, a purely surgical approach was not recommended and the surgical approach in the first instance was rejected by the patient.

Resectoscopic myomectomy is now widely acknowledged as an effective, safe, and minimally invasive surgical procedure for removing submucosal myomas classified as FIGO 0, 1, and 2 [11]. This technique has been established as the standard treatment for submucosal myomas since its introduction by Neuwirth and Amin in 1976 [11].

However, dealing with large submucosal fibroids and fibroids with a substantial intramural component (FIGO 1-2) presents a notable challenge for practitioners skilled in this procedure [11]. Such cases often come with operative complexities like bleeding or uterine perforation. For FIGO class 1-2

fibroids, a two-step procedure can be employed [9-11]. Initially, the protruding part of the fibroid is resected or ablated during the first hysteroscopic step [9-11]. Subsequently, the remaining intramural portion tends to migrate into the uterine cavity, leading to an increase in myometrial wall thickness. This allows for a complete and safe excision of the fibroid during the second hysteroscopic step [9-11].

Complete removal of FIGO class 1 and 2 fibroids is often hindered by their intramural component and size [9-11]. These limitations can be addressed by utilizing uterine artery embolization (UAE) to reduce the size of myomas before hysteroscopy [9-11]. This approach even enables the hysteroscopic treatment of fibroids that would otherwise be challenging to address [9-11].

Uterine artery embolization (UAE) is currently used in obstetrics and gynecology for managing uterine fibroids and controlling obstetric hemorrhage [6,9-11]. UAE serves as a uterus-preserving procedure for treating symptomatic myomas [9-11]. Embolization has shown good effectiveness in treating menometrorrhagia, with 86-92% of treated patients experiencing immediate resolution or marked improvement in this symptom [6-8]. The resolution or improvement of compressive disorders and painful symptoms, while requiring a longer duration, have been documented in 40-70% and 64-90% of patients, respectively [6].

The impact on the overall dimensions of the uterus and fibroids is also substantial [9-11]. The literature indicates a mean volumetric reduction of 50-60% for the uterus and 30-86% for the dominant fibroid [11,12]. This variation in dimensional reduction is primarily influenced by the fibroid's structural characteristics, particularly the interplay between vascular and stromal components and/or the quantity of extracellular matrix [12].

After performing UAE, a comprehensive assessment of clinical, radiological, and laboratory outcomes is necessary [6,8-11]. Our patient had notable improvement in painful symptoms and a reduction in the fibroid's size exceeding 50%. Fibroid embolization is commonly associated with the occurrence of collateral effects, collectively referred to as the "post-embolization syndrome". This syndrome includes pelvic pain (ischemic), fever (resulting from cytokine release and inflammatory reaction), and in rare cases, nausea and vomiting [9-11]. It affects 15-50% of patients and usually resolves within 1 week [9-11]. Despite the presence of adverse effects, most patients who undergo embolization can be discharged within 24-36 hours. They are prescribed oral analgesic therapy for a few days and typically resume normal activities within 8-10 days after the procedure [12].

The expulsion of a fibroid is the most common complication following UAE, occurring in over 10% of patients [11,12]. This

complication is attributed to a drastic reduction in the size of the fibroid, causing it to protrude into the uterine cavity [12,13]. It is more common with submucosal fibroids or intramural fibroids with a notable submucosal component. The peak incidence of this complication is 3 months after the procedure, with reported incidences ranging from 1.7% to 50%, depending on the patient cohort [12,13]. The main symptoms are pain, fever, recurrent bleeding, and discharge [13].

Small submucosal fibroids can be spontaneously expelled vaginally, while partial ejection of larger intramural/submucosal or transmural fibroids may require resectoscopy or vaginal myomectomy for removal [12]. The expulsion of an embolized fibroid, if not complicated by superinfection, represents a stage of uterine wall structural rearrangement in response to treatment and can be considered a form of cure [12,13]. In cases where necrotic components remain inside the cavity, the risk of infection increases. The required level of treatment depends on the patient's clinical status, ranging from no intervention or medical therapy to hysteroscopic extraction or even urgent hysterectomy [11-13]. Nulliparous women are more likely to require hysterectomy compared to parous women [14]. When compared to hysterectomy and myomectomy, UAE has a shorter hospital stay and fewer major complications, but a higher rate of reintervention [12-14]. Some studies suggest better symptom management with hysterectomy, but this procedure eliminates the possibility of future pregnancy [15].

The possible impact of this procedure on reproductive potential is important because most female candidates for embolization are aged 30-40 years [12]. There is little agreement regarding fertility status following uterine fibroid embolization. Approximations of post-myomectomy fertility status are 53.6-55.9%, but post-UAE fertility rates have not yet been quantified [15].

An important consideration in this context is radiation exposure during the procedure, given that the ovaries are among the most sensitive organs to radiation [12-15]. Exposure varies based on fluoroscopy duration, operator experience, and the number of angiographic sequences performed [15]. One plausible hypothesis is that ovarian hypoperfusion occurs because of nontarget embolization through collateral uterine ovarian circulation or a flow inversion in ovarian arteries after bilateral occlusion of uterine arteries. Post-embolization amenorrhea may also result from significant ischemic injury at the endometrial level, leading to atrophy or the formation of intrauterine synechiae due to chronic inflammation processes associated with tissue necrosis (Asherman's syndrome) [12]. Healthy pregnancies following UAE have been documented, although the exact fertility rate after UAE remains uncertain and is approximated at around 38.3% based on available published results [15].

In addition to UAE, our patient was prescribed medical therapy (Relugolix-CT) with the aim of reducing the symptoms and possibly further reducing the size of the fibroid. We emphasize the importance of the insertion of LNG-IUS, both for preventing unwanted pregnancies, with the associated risk of uterine rupture, and for its therapeutic effects. Thus, we highlight its dual role in prophylaxis and therapy.

Regarding the use of Relugolix, a gonadotropin-releasing hormone antagonist (GnRH receptor antagonist), there is consensus in the literature about its efficacy in reducing heavy menstrual bleeding, but not all authors agree on its effectiveness in reducing myoma size [16-20].

In this clinical case, we deemed it beneficial to combine Relugolix-CT with UAE to improve the woman's quality of life, reducing the symptoms, and to capitalize on the reported effect of reducing myoma volume as described by some authors [16,18-20].

A few recent case reports have explored the use of Relugolix combination therapy in treating uterine fibroids, highlighting its efficacy and potential complications, but ours is the first reporting the use of this medical treatment in combination of UAE prior to surgery.

Hudeček et al presented a case reports illustrating the use of Relugolix combination therapy (RCT) for uterine fibroid symptoms, including its role as a fertility-sparing option, its application in adenomyosis, and as a preoperative measure before surgery. It emphasizes RCT's effectiveness and safety in optimizing quality of life for women [21].

Acciardo et al reported a case involving a patient with polycystic ovary syndrome and multiple uterine fibroids. She was treated with a combination of Relugolix, estradiol, and norethisterone acetate, leading to significant symptom improvement, showing the potential of Relugolix combination therapy in managing complex gynecological conditions such as PCOS and fibroids [22].

Wada et al conducted an observational study focusing on submucosal leiomyomas treated with Relugolix. They identified specific characteristics of these fibroids that could lead to severe hemorrhage during treatment, emphasizing the need for careful patient selection and monitoring when using Relugolix in such cases [23].

Sasamori et al reported a case of a patient with adenomyosis and leiomyoma effectively treated with Relugolix in combination with Kamishoyosan, a traditional Japanese herbal medicine. The combined therapy resulted in symptom relief, suggesting a potential integrative approach for managing such conditions [24].

Ishizawa et al described a case where a pedunculated uterine leiomyoma prolapsed through the cervix during GnRH antagonist treatment with Relugolix. This rare complication highlights the importance of monitoring and preparedness for unexpected events during treatment [25].

These case reports illustrate the diverse applications and considerations of Relugolix combination therapy in treating uterine fibroids and related conditions. While the therapy shows promise, clinicians should remain vigilant regarding potential complications and tailor treatments to individual patient profiles. Moreover, none of the case reports in the literature discussed the combined use of Relugolix and UAE before surgery.

Conclusions

This case report confirms that large myomas with significant myometrial invasion can be safely and effectively managed using a one-step outpatient mini-hysteroscopic myomectomy following uterine artery embolization (UAE). This approach avoids the risks associated with major surgery, such as gastrointestinal or genitourinary injury, while enhancing patient safety and satisfaction. Combining UAE with Relugolix is a novel strategy that facilitates minimally invasive surgery, improves symptom

control, and optimizes outcomes. This personalized, multidisciplinary approach aligns with the “Safe Uterus” philosophy for managing benign conditions and offers a promising option for future treatment protocols.

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Statement

The clinical care was performed at the Department of Obstetrics and Gynecology and the Department of Radiology, Hospital Beauregard, AUSL Valleè d’Aoste, Aosta, Italy.

The clinical data and the literature review were performed at the Department of Gynecology and Obstetrics, University Hospital Maggiore della Carità, Novara, Italy.

Declaration of Figures’ Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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