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CASE REPORT

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Relugolix combination therapy in symptomatic adenomyosis and uterine fibroids: a case series

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ABSTRACT

Objective: To evaluate the clinical efficacy and safety of a once-daily oral fixed-dose combination of relugolix 40 mg, estradiol 1 mg, and norethisterone acetate 0.5 mg in women with symptomatic adenomyosis coexisting with uterine fibroids.

Methods: This case series included six women with uterine fibroids and concomitant adenomyosis, diagnosed by transvaginal ultrasound according to MUSA criteria. All patients received continuous treatment for 12 months. Clinical outcomes included changes in dysmenorrhea and pelvic pain assessed by the Visual Analogue Scale (VAS), menstrual blood loss evaluated through the Pictorial Blood Assessment Chart (PBAC), and hemoglobin levels. Ultrasonographic assessment measured uterine volume and adenomyosis-related features before and after treatment.

Results: All patients achieved complete resolution of dysmenorrhea and chronic pelvic pain, with VAS scores reduced to zero. Menstrual bleeding ceased in all cases (PBAC = 0), and hemoglobin levels improved after 12 months. Ultrasound examination demonstrated a reduction in uterine volume ranging from 8.6% to 58.3%, along with partial regression of direct adenomyotic features. No adverse events or treatment discontinuations were reported during follow-up.

Conclusions: Relugolix/estradiol/norethisterone acetate combination therapy was effective, well-tolerated, and associated with consistent clinical and sonographic improvement in women with adenomyosis and coexisting fibroids. Future larger-scale, controlled studies with extended follow-up are warranted to validate these findings.

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Adenomyosis; leiomyoma; relugolix; gonadotropin-releasing hormone; menorrhagia

Introduction

Adenomyosis is a prevalent uterine disorder that results in an enlarged uterus, heavy menstrual bleeding, chronic pelvic pain, and infertility, with a substantial negative impact on quality of life [1,2]. It often coexists with uterine fibromatosis, contributing to worsened clinical symptoms, as both disorders may alter the uterine architecture and impair normal myometrial function [3,4]. Current management strategies include surgery and medical therapies such as progestins, levonorgestrel-releasing intrauterine systems, and GnRH agonists [5–7]. However, these approaches are often limited by invasiveness, progesterone resistance, and adverse effects related to hypoestrogenism, which restrict long-term use [8–10]. In recent years, the introduction of oral GnRH antagonists has expanded therapeutic options. In particular, the fixed-dose combination of relugolix/estradiol/norethisterone acetate [Myfembree® (USA); Ryeqo® (EU)] has emerged as a promising alternative, offering effective symptom relief while mitigating adverse hypoestrogenic effects through add-back therapy [11]. Several studies have demonstrated that such therapies can lead to a rapid and significant reduction in uterine volume and fibroid size with improvement in pain and bleeding [12,13]. Nevertheless, evidence on the efficacy of this regimen for adenomyosis, particularly when coexisting with fibroids, remains limited, and data on medium-term outcomes with

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detailed sonographic assessment are scarce [14]. This case series reports on six patients with adenomyosis and coexisting uterine fibromatosis treated with relugolix/estradiol/norethisterone acetate, with prospective evaluation of ultrasound parameters, pain, and menstrual bleeding over 12 months.

Materials and methods

Study design and setting

This multicenter case series was conducted in accordance with the Declaration of Helsinki and reported in line with CARE (CAse REport) guidelines [15], adapted for small case series. The study was conducted across multiple centers in a real-world observational setting. It describes the clinical use of a fixed-dose combination therapy (Relugolix 40 mg, Estradiol 1 mg, and Norethisterone acetate 0.5 mg) in patients with symptomatic uterine fibroids and coexisting adenomyosis. Patients were consecutively included based on predefined eligibility criteria. Participating centers included the Department of Surgical Sciences, Division of Obstetrics and Gynecology, University Hospital of Cagliari; the Department of Health and Biomedical Sciences, University of Milan, Ospedale Macedonio Melloni; the Department of Obstetrics and Gynecology, Sapienza University of Rome, and the Gynecologic and Obstetric Unit of ARNAS Civico Di Cristina Benfratelli, Palermo.

Participants

This case series included six women aged ≥ 18 years with a confirmed diagnosis of symptomatic uterine fibroids coexisting with adenomyosis, established through transvaginal ultrasound. To be eligible, patients were required to have at least one uterine fibroid and ultrasonographic features of adenomyosis in accordance with the Morphological Uterus Sonographic Assessment (MUSA) criteria [16]. All patients presented with at least one clinically relevant symptom attributable to these conditions, including heavy menstrual bleeding, dysmenorrhea, and chronic pelvic pain. All patients were fully informed about the procedures and provided written consent.

Ultrasound imaging protocol

Ultrasound assessments were conducted by experienced sonographers using a GE Voluson E10 machine (GE Medical Systems, Zipf, Austria) equipped with a high-frequency endovaginal probe (5.0–9.0 MHz). Each examination was performed using two-dimensional (2D) grayscale ultrasound, complemented by color Doppler assessment and three-dimensional (3D) transvaginal imaging.

Fibroid size and volume were estimated by measuring three orthogonal diameters, anteroposterior (D1), longitudinal (D2), and transverse (D3), and using the conventional ellipsoid formula ($D1 \times D2 \times D3 \times 0.523$). Fibroids were also classified by location, according to the International Federation of Gynecology and Obstetrics (FIGO) classification system proposed by Munro et al. [17]. Vascularization was assessed using color Doppler imaging according to the MUSA group criteria [18] and graded using a semiquantitative subjective color score (1–3), reflecting increasing degrees of lesional blood flow.

Adenomyosis was evaluated through a systematic assessment of both direct and indirect sonographic features, in accordance with the MUSA criteria [16]. Direct signs included hyperechogenic islands, myometrial cysts, and echogenic sub-endometrial lines or buds. Indirect features, such as a globular uterus, asymmetrical thickening of the myometrium, fan-shaped acoustic shadowing, translesional vascularity, and irregular or disrupted appearance of the junctional zone, were also noted.

In cases of focal adenomyosis, lesion size was additionally estimated using bidimensional measurements and expressed as lesion area, calculated using the ellipse formula ($D1 \times D2 \times \pi/4$).

Clinical evaluation and outcome measures

At the initial evaluation (T0), clinical data were collected for each patient. This included demographic information such as age, body mass index (BMI), and parity, as well as details regarding previous

medical and surgical history, current pharmacological treatments, and relevant lifestyle factors. Menstrual blood loss was quantified using the Pictorial Blood Assessment Chart (PBAC) [19], with scores of 100 or higher considered indicative of heavy menstrual bleeding. Laboratory tests were performed to assess hemoglobin levels and iron status. Hemoglobin levels were monitored throughout follow-up, whereas serum iron, ferritin, and transferrin were assessed at baseline to evaluate iron deficiency and anemia.

Patients were also asked to report the severity of symptoms commonly associated with fibroids and adenomyosis. These included dysmenorrhea, chronic pelvic pain, dyspareunia, dyschezia, and dysuria, each of which was rated using a 10-point Visual Analogue Scale (VAS), where 0 represented no pain, and 10 corresponded to the most severe pain imaginable.

Treatment and follow-up

All patients were treated with a once-daily oral fixed-dose combination of Relugolix (40 mg), Estradiol (1 mg), and Norethisterone acetate (0.5 mg). Clinical assessments were performed every 3 months during the 1-year follow-up period, while a transvaginal ultrasound evaluation was scheduled at twelve months (T12) after treatment initiation.

Treatment response was assessed by changes in PBAC scores, hemoglobin levels, and pain intensity scores. Ultrasound was used to evaluate changes in uterine volume, fibroid size, and adenomyosis-related features. Safety and tolerability were monitored through clinical examination and routine laboratory investigations, including liver and renal function tests. Any adverse events occurring during the treatment period were documented every three months during the follow-up.

Case series

The clinical profiles of the patients, their sonographic findings, and the treatment outcomes are comprehensively detailed in Tables 1 and 2. Detailed longitudinal data for PBAC scores, pain intensity (VAS), and hemoglobin levels at each follow-up time point are reported in Supplementary Table S1.

Table 1. Demographic and clinical characteristics of patients.

Characteristic	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Age (years)	43	37	49	48	50	33
Body mass index (kg/m^2)	25	18	21	26	24	30
Ethnicity	Caucasian	Caucasian	Caucasian	Caucasian	Caucasian	Caucasian
Parity	0	0	2	2	0	0
Adenomyosis type	Moderate focal adenomyosis of the posterior wall type II-III	Severe diffuse adenomyosis of the anterior wall type I-II-III	Severe diffuse adenomyosis of the anterior wall type I-II	Severe diffuse adenomyosis of the posterior wall type II-III	Severe diffuse adenomyosis of the posterior wall type II-III	Severe diffuse adenomyosis of the anterior wall type II-III
Adenomyosis direct signs	-Hyperechogenic islands	-Hyperechogenic islands - Echogenic sub-endometrial lines and buds -Myometrial cysts	-Hyperechogenic islands -Echogenic sub-endometrial lines and buds -Myometrial cysts	Hyperechogenic islands -Echogenic sub-endometrial lines and buds	Hyperechogenic islands -Echogenic sub-endometrial lines and buds	Hyperechogenic islands -Echogenic sub-endometrial lines and buds
Adenomyosis indirect signs	-Globular uterus -Asymmetrical myometrial thickening -Fan-shaped shadowing -Translesional vascularity	-Globular uterus -Asymmetrical myometrial thickening -Fan-shaped shadowing -Irregular junctional zone -Translesional vascularity	-Globular uterus -Asymmetrical myometrial thickening -Fan-shaped shadowing - Irregular junctional zone -Translesional vascularity	-Globular uterus -Asymmetrical myometrial thickening -Irregular junctional zone -Translesional vascularity	-Globular uterus -Asymmetrical myometrial thickening -Irregular junctional zone -Translesional vascularity	-Asymmetrical myometrial thickening -Irregular junctional zone -Translesional vascularity

Abbreviations: BMI = body mass index; Type I = adenomyosis involving the inner myometrium (junctional zone); Type II = adenomyosis involving the middle myometrium; and Type III = adenomyosis involving the outer myometrium.

Table 2. Comparison of procedure outcomes before and after treatment.

Procedure outcomes	Before treatment						After treatment (T12)					
	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Uterine volume (cm^3)	233.94	247.9	233	213	187	53	109.83	178.91	213	111	78	45
Myoma type and volume (cm^3)	FIGO 6: 10.6;FIGO 4: 16.95	FIGO 4: 1.54	FIGO 6: 0.8; FIGO 5: 1.13	FIGO 3:1.77	FIGO 4:1.4	FIGO 2-5: 9.2	FIGO 6: 6.09; FIGO 4: 6.8	FIGO 4: 0.47	FIGO 6: 0.8; FIGO 5: 1.02	FIGO 3:1.4	FIGO 4: 0.28	FIGO 2-5: 8.6
Myoma color score (grade)	FIGO 6: 3; FIGO 4: 3	FIGO 4: 3	FIGO 6: 2; FIGO 5: 2	FIGO 3:1	FIGO 4:1	FIGO 2-5:2	FIGO 6: 2; FIGO 4: 2	FIGO 4: 2	FIGO 6: 1; FIGO 5: 1	FIGO 3:1	FIGO 4: 1	FIGO 2-5: 2
Focal adenomyosis lesion (mm)	50 × 49	N/A	N/A	N/A	N/A	N/A	49 × 35	N/A	N/A	N/A	N/A	N/A
PBAC score	25	300	264	160	50	60	0	0	0	0	0	0
Dysmenorrhea (VAS)	8	8	9	8	9	9	0	0	0	0	0	0
Chronic pelvic pain (VAS)	0	7	8	6	4	7	0	0	0	0	0	0
Dyspareunia (VAS)	0	7	0	5	6	6	0	0	0	0	0	6
Dyschezia (VAS)	0	0	0	0	0	0	0	0	0	0	0	0
Dysuria (VAS)	0	0	0	2	0	0	0	0	0	0	0	0
Serum Hb (g/dl)	7.1	8.0	9.6	9.8	10	11	12.3	11.5	11.0	11.3	12	11.2

Abbreviations: cm^3 = cubic centimeters; FIGO = International Federation of Gynecology and Obstetrics; mm = millimeters; T12 = 12-month follow-up; PBAC = pictorial blood assessment chart; VAS = visual analogue scale; Hb = Hemoglobin; and g/dL = grams per deciliter; N/A = Not applicable.

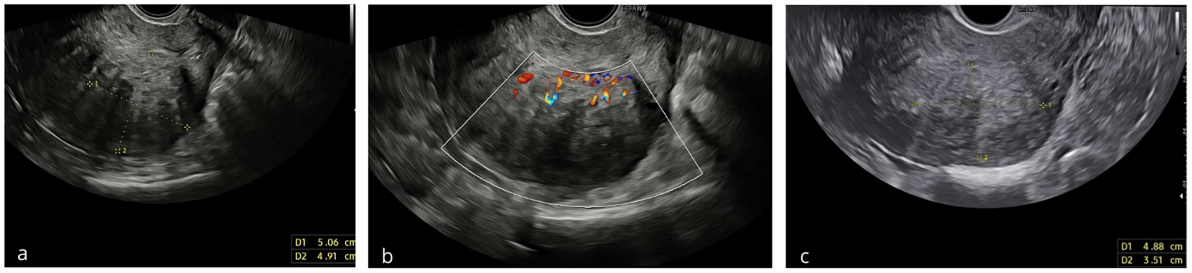

Figure 1. Transvaginal ultrasound images of the uterus in Case 1. (a) Baseline two-dimensional grayscale image showing a focal adenomyotic lesion in the posterior myometrium. The lesion appears heterogeneous with multiple hyperechogenic islands, consistent with focal adenomyosis. (b) Color Doppler imaging at baseline demonstrates moderate translesional vascularity within the adenomyotic area. (c) Follow-up grayscale image at 12 months showing a reduction in lesion size and overall improvement in echotexture, reflecting partial resolution of direct signs of adenomyosis following 12 months of treatment.

Case 1

This case concerns a 43-year-old nulliparous Caucasian woman with a body mass index of 25 kg/m^2 and a prior history of laparoscopic myomectomy for uterine fibroids. She presented with longstanding polymenorrhea, characterized by menstrual cycles every 15 days, accompanied by moderate menstrual blood loss (PBAC 25) and severe dysmenorrhea rated 8/10 on the visual analogue scale (VAS). She denied chronic pelvic pain, dyspareunia, dyschezia, or urinary symptoms. Her clinical history was notable for iron-deficiency anemia, with a hemoglobin level of 7.1 g/dL at baseline.

Transvaginal ultrasound revealed a globular-shaped uterus with a calculated volume of 233.94 cm^3. A focal adenomyotic lesion measuring 50 × 49 mm was identified in the posterior myometrium (Figure 1a). According to the MUSA criteria, the lesion was classified as focal adenomyosis of moderate severity involving both the inner and outer posterior myometrial layers (type II–III). The only direct sonographic feature observed was the presence of hyperechogenic islands, while indirect signs included asymmetrical thickening of the myometrium, fan-shaped acoustic shadowing, and translesional vascularity (Figure 1b).

Two fibroids were also identified: a subserosal fundal FIGO type 6 myoma measuring 10.6 cm^3 (color score 3), and a posterior intramural FIGO type 4 myoma measuring 16.95 cm^3 (color score 3).

In light of ongoing symptoms and poor response to previous hormonal therapies, the patient was started on once-daily oral treatment with a fixed-dose combination of Relugolix 40 mg, Estradiol 1 mg, and Norethisterone acetate 0.5 mg. At the 12-month follow-up, the patient reported complete symptom resolution, with VAS scores reduced to 0 across all domains, and amenorrhea was confirmed by a PBAC score of 0. Hemoglobin improved to 12.3 g/dL. Ultrasound follow-up demonstrated a marked reduction in uterine volume to 109.83 cm^3. Both fibroids showed reduced vascularity (color score 2) and decreased volume, while maintaining stable morphology. The focal adenomyotic lesion decreased in size to 49 × 35 mm, representing an approximate 30% reduction in lesion area (Figure 1c). The indirect sonographic features of adenomyosis persisted. The treatment was well-tolerated, and the patient reported no adverse effects.

Case 2

This case involves a 37-year-old nulliparous Caucasian woman with a body mass index of 18 kg/m^2, presenting with severe cyclic pelvic pain and sexual dysfunction. She reported high-intensity dysmenorrhea (VAS 8), chronic pelvic pain (VAS 7), and deep dyspareunia (VAS 7). Menstrual blood loss was markedly elevated (PBAC 300), and her baseline hemoglobin was 8.0 g/dL. Previous management with progestins and tranexamic acid had not yielded satisfactory results.

Transvaginal ultrasound revealed a globular uterus with a volume of 247.9 cm^3 and multiple MUSA-defined sonographic features of severe diffuse adenomyosis involving the anterior wall (type I–II–III) (Figure 2a). Direct signs included hyperechogenic islands, echogenic sub-endometrial lines and buds, and myometrial cysts. Indirect signs included a globular uterus, asymmetrical myometrial thickening, fan-shaped shadowing, irregular junctional zone, and translesional vascularity (Figure 2b and c). A single fibroid FIGO 4 was noted (1.54 cm^3, color score 3).

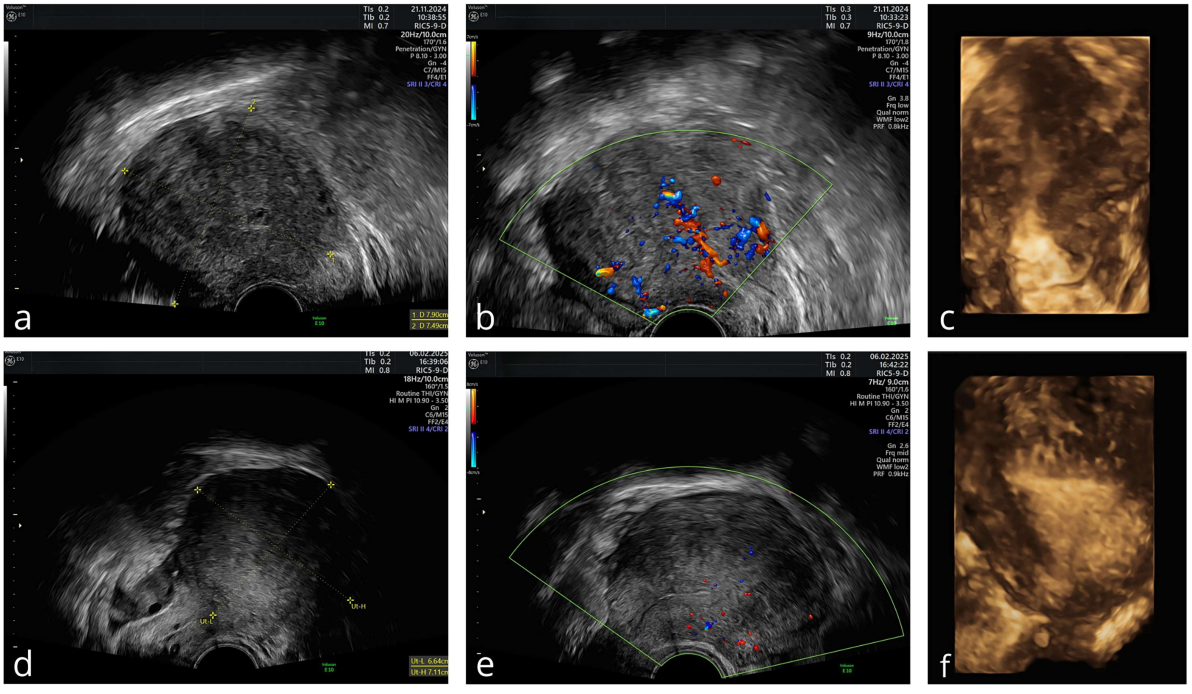

Figure 2. Transvaginal ultrasound evaluation of the uterus in Case 2. (a) Baseline two-dimensional grayscale image showing a markedly enlarged, globular uterus with diffuse myometrial heterogeneity. Notable direct signs of adenomyosis are present, including hyperechogenic islands, subendometrial echogenic lines and buds, and small myometrial cysts. (b) Color Doppler ultrasound at baseline revealed scattered intramyometrial vascularity (color score 3). (c) Baseline 3D ultrasound reconstruction showing an irregular junctional zone with a distorted endometrial-myometrial interface. (d) Follow-up grayscale ultrasound after 12 months of treatment, showing a reduction in uterine dimensions and improved myometrial echotexture. (e) Color Doppler at follow-up demonstrating reduced vascularization (color score 2). (f) 3D ultrasound at 12 months displaying a less distorted uterine contour and partial restoration of the junctional zone.

After initiating Relugolix-based combination therapy, the 12-month assessment showed complete resolution of pelvic pain and dyspareunia (VAS 0), cessation of menstrual bleeding (PBAC 0), and increased hemoglobin to 11.5 g/dL. The uterine volume was reduced to 178.91 cm^3. The fibroid showed a decreased color score (2) and a reduction in volume (0.47 cm^3). At follow-up, direct signs of adenomyosis appeared reduced, whereas indirect signs persisted with similar characteristics (Figure 2d–f). The patient reported excellent tolerability, with no treatment-related adverse effects.

Case 3

A 49-year-old multiparous Caucasian woman (BMI 21 kg/m^2) presented with severe dysmenorrhea (VAS 9), chronic pelvic pain (VAS 8), and heavy menstrual bleeding (PBAC 264). She had previously undergone multiple medical therapies over six years (estroprogestins, progestins, GnRH analogues, and Levonorgestrel-Releasing Intrauterine Device) without substantial clinical improvement, and had declined surgical myomectomy due to concerns regarding invasiveness.

At baseline, the patient fulfilled the MUSA criteria for severe diffuse adenomyosis of the anterior wall (type I–II), with the presence of three direct signs: hyperechogenic islands, echogenic subendometrial lines and buds, and myometrial cysts (Figure 3a). Indirect signs included a globular uterus, asymmetrical myometrial thickening, fan-shaped shadowing, irregular junctional zone, and translesional vascularity (Figure 3b). Baseline laboratory investigations revealed anemia (Hb 9.6 g/dL). A transvaginal ultrasound showed a globular, enlarged uterus with a calculated volume of 233.0 cm^3 and irregular myometrial

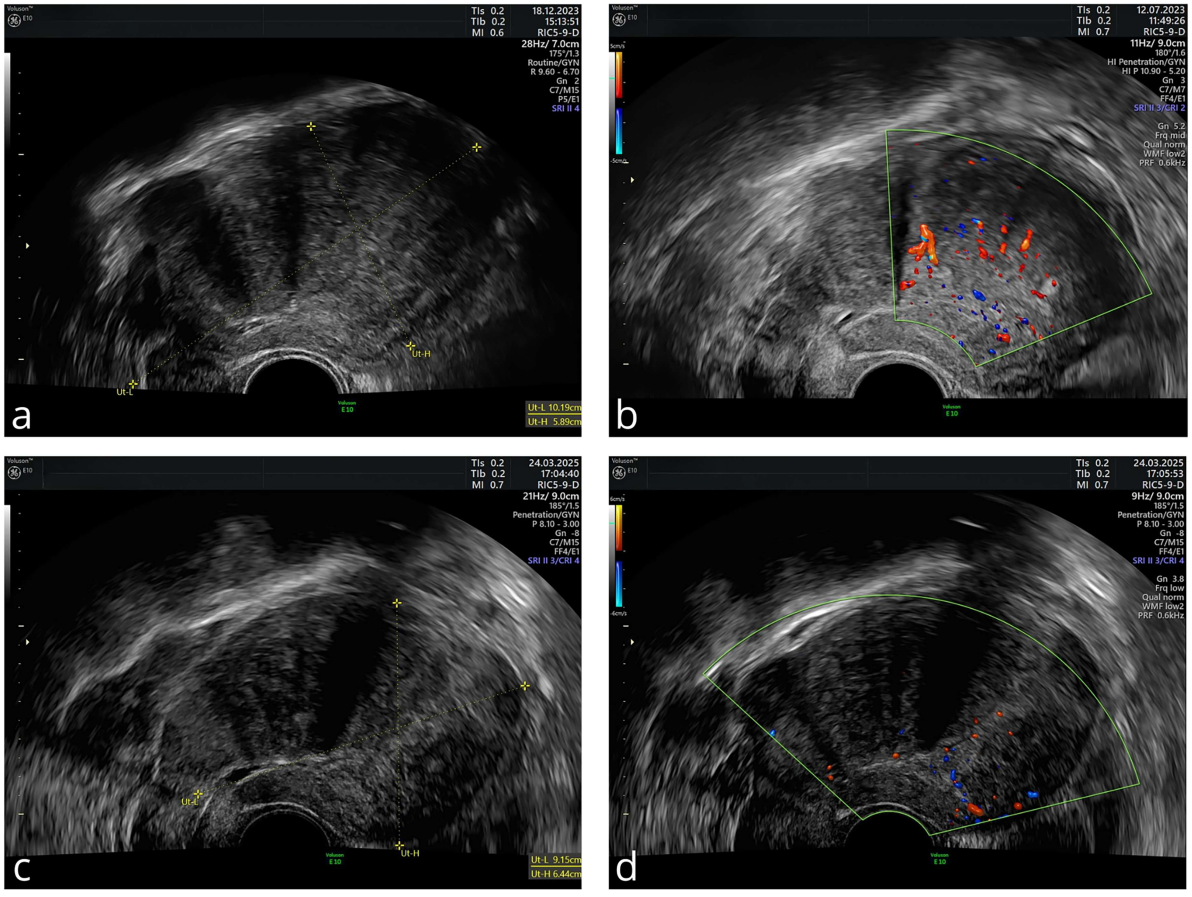

Figure 3. Transvaginal ultrasound evaluation of the uterus in Case 3. (a) Baseline grayscale image showing an enlarged globular uterus with anterior wall thickening and heterogeneous myometrial echotexture. Direct signs of adenomyosis are visible, including hyperechogenic islands, echogenic sub endometrial lines and buds, and small myometrial cysts. (b) Baseline color Doppler image demonstrating marked translesional vascularity (color score 3). (c) Follow-up grayscale ultrasound at 12 months showing a reduction in uterine volume and slightly improved homogeneity of the myometrial texture. (d) Follow-up Doppler image revealing decreased vascularization (color score 2) after 12 months of therapy.

echotexture. Color Doppler revealed scattered vessels with a comb-like distribution and a color score of 3. Two posterior wall fibroids were also noted: a FIGO type 6 myoma (0.8 cm^3, color score 2) and a FIGO type 5 myoma (1.13 cm^3, color score 2).

The patient was started on daily oral therapy with Relugolix 40 mg, Estradiol 1 mg, and Norethisterone acetate 0.5 mg. At the 12-month follow-up, she reported complete resolution of all symptoms (VAS 0), cessation of bleeding (PBAC 0), and hemoglobin improvement to 11.0 g/dL. Ultrasound confirmed a reduction in uterine volume to 213.00 cm^3. The fibroids remained stable in size, with the FIGO 6 lesion still measuring 0.8 cm^3, and the FIGO 5 lesion slightly reduced to 1.02 cm^3, both showing reduced vascularity (color score 1). Direct signs of adenomyosis appeared reduced, whereas indirect signs persisted, albeit with decreased intensity (Figure 3c and d). The therapy was well-tolerated, with no adverse events, and the patient expressed high satisfaction with the clinical outcome.

Cases 4–6

Three additional patients affected by symptomatic adenomyosis associated with uterine fibroids were treated with the fixed-dose combination of Relugolix 40 mg, Estradiol 1 mg, and Norethisterone acetate 0.5 mg. All presented with moderate to severe menstrual pain and varying degrees of dyspareunia and chronic pelvic discomfort.

Case 4 concerned a 48-year-old multiparous woman with a history of endometriosis, adenomyosis, and previous laparoscopic removal of a right ovarian endometrioma. At baseline, she reported severe dysmenorrhea (VAS 8/10), chronic pelvic pain (6/10), moderate dyspareunia (VAS 5/10), and mild dysuria (VAS 2/10), with heavy menstrual bleeding (PBAC 160) and anemia (Hb 9.8 g/dL). Ultrasound revealed a globular uterus (213 cm^3) with a small intramural fibroid (FIGO 3, 1.77 cm^3, color score 1) and severe diffuse adenomyosis of the posterior wall (type II–III), characterized by hyperechogenic islands, echogenic sub-endometrial lines and buds, asymmetrical myometrial thickening, irregular junctional zone, and translesional vascularity. After 12 months, she achieved complete resolution of all symptoms (VAS 0, PBAC 0) and normalization of hemoglobin (11.3 g/dL), with a reduction in uterine volume to 111 cm^3.

Case 5 involved a 50-year-old nulliparous woman presenting with chronic pelvic pain, severe dysmenorrhea (VAS 9/10), and deep dyspareunia (VAS 6/10). Menstrual bleeding was moderate (PBAC 50) and hemoglobin was 10 g/dL. Transvaginal ultrasound showed a globular uterus (187 cm^3) with an intramural myoma (FIGO 4, 1.4 cm^3, color score 1) and severe diffuse adenomyosis of the posterior wall (type II–III), showing hyperechogenic islands, echogenic sub-endometrial lines and buds, asymmetrical myometrial thickening, irregular junctional zone, and translesional vascularity. After 12 months, she reported complete symptom remission (VAS 0, PBAC 0) and hemoglobin increase to 12 g/dL. Uterine volume was reduced to 78 cm^3, and fibroid volume decreased to 0.28 cm^3 with unchanged vascularity.

Case 6 referred to a 33-year-old nulliparous woman with a history of endometriosis and previous laparotomic removal of a right ovarian endometrioma. She had previously undergone hormonal therapy with norethisterone acetate (NETA) 2.5 mg daily without clinical benefit. She reported severe dysmenorrhea (VAS 9/10), chronic pelvic pain (VAS 7/10), and dyspareunia (VAS 6/10). Baseline PBAC was 60 and hemoglobin was 11 g/dL. Ultrasound showed a uterine volume of 53 cm^3 and a single intramural fibroid (FIGO 2–5, 9.2 cm^3, color score 2) with severe diffuse adenomyosis of the anterior wall (type II–III), displaying hyperechogenic islands, echogenic sub-endometrial lines and buds, asymmetrical myometrial thickening, irregular junctional zone, and translesional vascularity. After 12 months, dysmenorrhea and pelvic pain resolved completely (VAS 0), menstrual bleeding ceased (PBAC 0), and hemoglobin rose to 11.2 g/dL. Dyspareunia persisted (VAS 6) despite the resolution of other symptoms. Uterine volume was 45 cm^3, and fibroid vascularity remained stable.

Discussion

This case series highlights the potential of relugolix/estradiol/norethisterone acetate (R/E/N) combination therapy as an effective medical alternative for women suffering from symptomatic adenomyosis coexisting with uterine fibroids. Although the efficacy of this combination has been previously demonstrated in patients with uterine fibroids, its impact on adenomyotic lesions, especially when coexisting with

leiomyomas, remains underexplored [4]. Our prospective evaluation of six patients provides preliminary evidence supporting its role in symptom control, improvement in hemoglobin levels reflecting correction of anemia, and sonographic changes over a 12-month period.

The clinical impact of R/E/N was significant across all six cases. Complete resolution of dysmenorrhea and chronic pelvic pain was observed at 12 months in all symptomatic patients, while dyspareunia persisted in one case (Case 6). Amenorrhea was achieved in all cases, accompanied by an overall increase in hemoglobin levels, with values improving from moderate or severe anemia to near-normal range. These findings are consistent with results from the LIBERTY and SPIRIT trials, which established the efficacy of R/E/N in reducing bleeding associated with uterine fibroids and pain associated with endometriosis, respectively [4,20].

The effectiveness of R/E/N in endometriosis is particularly relevant in this context, as endometriosis shares key pathophysiological features with adenomyosis. Both conditions are characterized by estrogen dependence, a pro-inflammatory microenvironment, and progesterone resistance [21,22], which together contribute to disease progression. In this setting, aberrant estrogen signaling drives ectopic endometrial proliferation, while impaired progesterone responsiveness reduces anti-proliferative regulation [23,24]. Targeting these mechanisms, therefore, represents a rational therapeutic strategy. Accordingly, R/E/N combination therapy exerts its effects through a dual mechanism, combining central suppression of gonadotropin release via relugolix with hormonal stabilization provided by estradiol and norethisterone acetate. This integrated approach allows effective symptom control while maintaining endocrine balance and minimizing hypoestrogenic adverse effects [8,20].

The pharmacological profile of relugolix further supports its clinical use, as it enables immediate suppression of gonadotropin release without the initial flare effect associated with GnRH agonists, offering a more favorable safety and tolerability profile [25]. In addition, the inclusion of hormonal add-back therapy in the fixed-dose formulation helps to maintain bone mineral density and minimize vasomotor symptoms, crucial considerations for long-term treatment in premenopausal women [26].

From an imaging perspective, treatment response appeared more heterogeneous. A reduction in total uterine volume was observed, ranging from 8.6% to 58.3%, even in patients with substantial baseline enlargement, such as Cases 2 (247.9 cm^3) and 3 (233.0 cm^3). In contrast, fibroid volumes showed variable changes across cases, ranging from minimal variation to marked reductions, without a consistent relationship with overall uterine volume changes. This apparent dissociation between symptom relief and fibroid size reduction mirrors findings from the LIBERTY 1 and 2 trials, where relugolix combination therapy led to significant improvements in heavy menstrual bleeding, despite not consistently reducing fibroid volume [4].

In parallel, direct signs of adenomyosis, such as hyperechogenic islands and myometrial cysts, tended to regress during treatment. A similar pattern was reported by Yamanaka et al. [12], who observed greater regression of adenomyotic lesions compared to coexisting fibroids during relugolix-based therapy. This differential tissue response likely reflects underlying biological differences, as adenomyotic tissue typically shows elevated estrogen receptor expression and diminished progesterone sensitivity, making it more susceptible to estrogen suppression [27], whereas fibroids are characterized by a more rigid extracellular matrix and lower hormonal responsiveness, contributing to their structural persistence [28,29].

By contrast, indirect signs of adenomyosis, such as asymmetrical myometrial thickening and fan-shaped shadowing, tended to persist throughout treatment, likely reflecting chronic fibrotic remodeling rather than active disease. This distinction is consistent with current models of adenomyosis progression, which describe an initial phase of glandular infiltration followed by irreversible architectural changes in the myometrium such as localized fibrosis and muscular hyperplasia [30,31]. Thus, while symptom improvement often parallels the resolution of direct signs, the persistence of indirect features on ultrasound may reflect long-standing tissue remodeling.

Another important consideration is the apparent variability in treatment response between focal and diffuse forms of adenomyosis. Although based on a limited sample, all patients achieved complete clinical remission, regardless of disease phenotype. However, imaging findings differed. The focal lesion in Case 1 showed a quantifiable reduction in size, representing a clear imaging endpoint. In contrast, patients with diffuse disease (Cases 2–6) demonstrated improvement primarily through symptom resolution and partial regression of direct sonographic features, while changes in uterine volume were variable and less specific.

These findings suggest that, although both phenotypes respond favorably to treatment, the evaluation of therapeutic response should be tailored according to disease type. In focal adenomyosis, lesion size may serve as an objective parameter for follow-up, whereas in diffuse disease, a combined assessment integrating clinical outcomes and qualitative sonographic changes may be more appropriate.

From a safety standpoint, the treatment was well tolerated in all six cases, with no adverse events or clinically relevant laboratory abnormalities observed. This favorable profile contrasts with the well-known side effects of GnRH agonists, which are often associated with hypoestrogenic symptoms and limited long-term tolerability [32] and further supports the use of GnRH antagonists combined with add-back therapy as a viable alternative.

Finally, the significant improvement in hemoglobin levels observed across all cases represents a clinically meaningful systemic benefit. By effectively reducing menstrual blood loss, R/E/N not only alleviates local symptoms but also contributes to correcting anemia and its broader impact on fatigue, physical capacity, and overall quality of life.

Despite these encouraging results, several limitations should be acknowledged. The limited sample size and the descriptive nature of this case series restrict the generalizability of the results. Furthermore, although the 12-month follow-up offers valuable longitudinal insights, longer-term studies are needed to assess the long-term sustainability of these improvements beyond the one-year period.

Conclusion

This case series provides preliminary evidence that relugolix/estradiol/norethisterone acetate therapy may offer effective and sustained symptom control, along with measurable sonographic and hematological improvement in patients with adenomyosis and coexisting fibroids. Future larger-scale, controlled studies with extended follow-up are warranted to validate these findings.

Author contributions

CRediT: **Stefania Saponara:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing; **Maurizio Nicola D'Alterio:** Conceptualization, Data curation, Investigation, Methodology, Writing – original draft, Writing – review & editing; **Stefano Di Michele:** Investigation, Resources, Visualization, Writing – original draft; **Caterina Chilà:** Methodology, Resources, Visualization; **Antonio Maiorana:** Investigation, Resources, Validation; **Michele Vignali:** Investigation, Resources, Validation; **Ludovico Muzii:** Investigation, Resources, Validation; **Stefano Angioni:** Conceptualization, Project administration, Resources, Supervision, Validation, Writing – review & editing.

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Ethics approval

This study is an observational case series based on data collected during routine clinical practice. This type of study does not require Ethics Committee approval.

Consent to participate

Informed consent was obtained from all individual participants included in the study.

Consent to publish

All patients provided written informed consent for the use of their anonymized clinical data and for publication.

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