EDITORIAL

# Relugolix combination therapy: A novel hormonal treatment for AUB associated with uterine fibroids

Oral relugolix combination therapy (relugolix, estradiol, norethindrone acetate) was effective in controlling excess bleeding caused by uterine fibroids in the majority of treated women, with few adverse effects

**Robert L. Barbieri, MD**
Chair Emeritus, Department of Obstetrics and Gynecology
Interim Chief, Obstetrics
Brigham and Women's Hospital
Kate Macy Ladd Distinguished Professor of Obstetrics, Gynecology and Reproductive Biology
Harvard Medical School
Boston, Massachusetts

When gonadotropin-releasing hormone (GnRH) agonist and antagonist peptide medications were first approved for use in the 1980s and 1990s, the available agents could only be administered by injection or nasal spray. The innovative development of orally active, non-peptide GnRH antagonists, including relugolix and elagolix (**FIGURE 1**), is a major breakthrough in women's health. Orally active GnRH antagonists provide gynecologists with a unique way to regulate hypothalamic-pituitary-ovarian-uterus function. GnRH antagonists bind to the pituitary GnRH receptor, reducing pituitary secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH). In turn, reduction in LH and FSH suppresses ovarian follicle development, reducing ovarian secretion of estradiol and progesterone. The uterine endometrium becomes less active in response to low levels of estradiol and progesterone, resulting in oligomenorrhea or amenorrhea. The hypoestrogenic adverse effects of GnRH antagonist treatment, including bone loss and vasomotor symptoms can be minimized by adding back a low dose of estrogen and progestin, such as oral estradiol 1 mg and norethindrone acetate 0.5 mg.

Recently, the US Food and Drug Administration (FDA) approved oral relugolix combination therapy (Myfembree, Myovant Sciences and Pfizer Inc; relugolix 40 mg, estradiol 1 mg, and norethindrone acetate 0.5 mg) once daily for the treatment of abnormal uterine bleeding (AUB) associated with uterine leiomyomata (fibroids) in premenopausal women for up to 24 months.[1] This editorial will focus on key clinical issues when using relugolix combination therapy.

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## Relugolix combination treatment is superior to placebo for AUB from fibroids

In 2 clinical trials, 770 women with symptomatic uterine fibroids were randomly assigned to 1 of 3 groups[2]:

- placebo for 24 weeks
- relugolix combination therapy (consisting of relugolix 40 mg, estradiol 1 mg, and norethindrone acetate 0.5 mg) daily for 24 weeks
- relugolix monotherapy (40 mg daily for 12 weeks) followed by relugolix combination therapy for 12 additional weeks (delayed combination therapy group).

The women's mean age was approximately 42 years, and they had a mean menstrual blood loss at baseline of approximately 230 mL and mean uterine volume by ultrasound measurement of 408 $cm^3$.[2] Prior to entry into the study all the women had an endometrial biopsy and a transvaginal ultrasound study of the pelvis. Women with a baseline bone

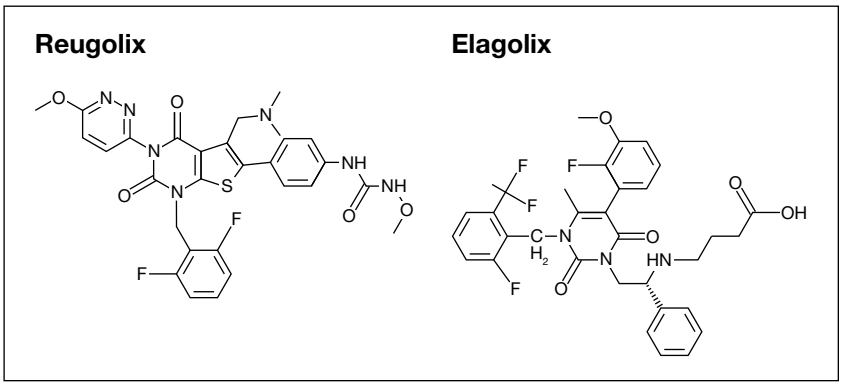
mineral density Z-score of less than -2.0 at the spine, total hip, or femoral neck were excluded from the study because of low bone mass.[2]

At 24 weeks of treatment, approximately 72% of the women in the relugolix combination therapy groups had less than 80 mL of menstrual blood volume loss and ≥50% reduction in menstrual blood loss from baseline compared with 17% of women in the placebo group.[2] At 8 weeks of treatment mean percent changes in menstrual blood loss from baseline were approximately 80% and 20% for the women receiving relugolix combination and placebo, respectively. Those differences persisted from 8 weeks through 24 weeks of treatment.[1] In the last 35 days of treatment, amenorrhea was reported by approximately 51% and 4.5% of women receiving relugolix combination or placebo treatment, respectively.[2] Compared with the placebo group, the relugolix combination groups reported significant improvement in bleeding and pelvic discomfort and had a higher hemoglobin concentration. Compared with placebo, relugolix combination treatment resulted in a greater percentage decrease in uterine volume (-12.9% vs +2.2%, respectively; $P < .001$).[2]

## Relugolix combination treatment is associated with fewer side effects than relugolix monotherapy

Compared with relugolix combination therapy, women treated with relugolix monotherapy for 12 weeks followed by 12 weeks of relugolix combination therapy lost more bone density as measured by dual-energy X-ray absorptiometry and reported more vasomotor symptoms. This is an expected finding because GnRH antagonist monotherapy is known to significantly reduce ovarian estradiol and progesterone levels, causing bone loss and vasomotor symptoms. Relugolix combination treatment minimizes bone density loss and vasomotor symptoms because the combination of estradiol and norethindrone helps to preserve bone density and reduce hot flashes. Based on these and other findings, the FDA approved relugolix combination therapy for up to 24 months of treatment.[1]

**FIGURE 1** Chemical structures of relugolix and elagolix




### Contraindications

Contraindications to relugolix combination therapy include: 1) pregnancy, 2) undiagnosed abnormal uterine bleeding, 3) current or personal history of breast cancer or other hormone-sensitive cancer, 4) known osteoporosis, 5) liver disease, 6) high risk of thrombosis, and 7) hypersensitivity to components of the medication.[1]

### Adverse reactions

Serious adverse reactions were reported by 3.1% and 2.3% of women treated with the relugolix combination and placebo, respectively. Women taking relugolix combination reported the following adverse effects: 10.6% hot flashes, 6.3% AUB, 3.5% alopecia, and 3.1% decreased libido. Women taking placebo reported the following adverse effects: 6.6% hot flashes, 1.2% AUB, 0.8% alopecia, and 0.4% decreased libido. Among women taking relugolix combination, the following events occurred, each reported once by different women: myoma expulsion with menorrhagia, myoma prolapse without menorrhagia, cholecystitis, and pelvic pain.[1]

### Bone loss

In women taking relugolix combination or placebo for 6 months, lumbar spine bone density change from baseline, as measured by DEXA, were -0.23% and +0.18%, respectively.[1] After 12 months of relugolix combination treatment, lumbar spine bone density had decreased by -0.8% from baseline. These changes in lumbar bone density are minimal, and in my opinion of no clinical importance.

### Reported mental health effects

Compared with placebo, more women taking relugolix combination reported depression, depressed mood, or mood swings (2.4% vs 0.8%), irritability (2.4% vs 0%), and anxiety (1.2% vs 0.8%).[1]

## Options for the treatment of AUB caused by fibroids

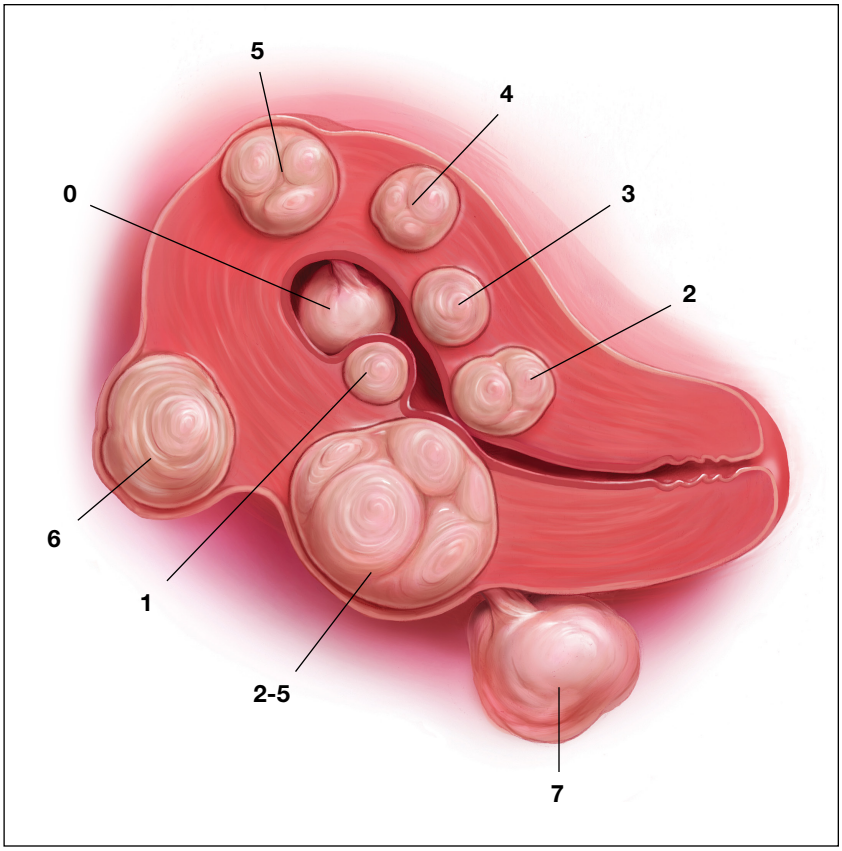
There are many options for the treatment of AUB caused by fibroids,

including surgical, hormonal, and nonhormonal therapies. Women with bothersome fibroids strongly prefer to be involved in the decision-making process and select the treatment plan that is best for their situation.[3] The patient's preferences can be explored by discussing the main benefits and common complications and side effects of each treatment option.

Surgical options for the treatment of AUB caused by fibroids include, but are not limited to, hysterectomy (laparoscopic, vaginal, or laparotomy), myomectomy (hysteroscopic, laparoscopic, or laparotomy), uterine artery embolization, focused ultrasound surgery, radiofrequency ablation, cryomyolysis, endometrial ablation, and occlusion of the uterine arteries.[4] The FIGO classification system provides a consensus nomenclature for describing fibroid location (see **FIGURE 2**).[5] The selection of a treatment option is greatly influenced by the location of the fibroids in the uterus.[6] Most experts recommend hysteroscopic myomectomy to treat Type 0 and Type 1 fibroids causing AUB.[6] For Type 2 fibroids, hysteroscopic myomectomy, if technically feasible, is associated with a high rate of resolution of AUB with minimal complications. Hormonal treatment of Type 0 and Type 1 fibroids may result in red degeneration of the fibroid with significant menorrhagia.[7,8] In my practice, I generally advise patients that hysteroscopic myomectomy is the first-line treatment option for Types 0, 1, and 2 fibroids causing AUB.

The FDA has approved the hormonal options of relugolix combination therapy (Myfembree)[2] and elagolix combination therapy (Oriahnn)[9,10] for the treatment of AUB associated with fibroids. Of note, elagolix combination therapy contains the same daily dose of estradiol (1 mg) and norethindrone acetate (0.5 mg) as relugolix combination therapy. Relugolix and elagolix combination therapy for fibroids are good options for women who have FIGO Type 2 to 5 fibroids and who prefer a nonsurgical option. If GnRH antagonist combination therapy results in a meaningful reduction in AUB, treatment can be continued for up to 2 years. If the patient reports an insufficient decrease in AUB, an alternative surgical, hormonal, or nonhormonal option can be offered.

**FIGURE 2** **FIGO anatomical classification of uterine leiomyomata**[5]




0–pedunculated, intracavitary fibroid; 1–submucosal fibroid, < 50% intramural; 2–submucosal, ≥ 50% intramural; 3–contact with endometrium, 100% intramural; 4–intramural; 5–subserosal, ≥ 50% intramural; 6–subserosal, <50% intramural; 7–pedunculated. When two numbers are given to describe the location of a fibroid, the first number refers to the relationship with the endometrium and the second number refers to the relationship with the serosa.

ILLUSTRATION: KIMBERLY MARTENS FOR OBG MANAGEMENT

Other hormonal treatments that may reduce AUB due to fibroids include combination estrogen-progestin contraceptives,[11] the levonorgestrel-releasing intrauterine device (LNG-IUD),[12] progestins, and leuprolide.[13] Leuprolide plus iron therapy is approved by the FDA for improving red blood cell concentration prior to surgery in women with fibroids, AUB, and anemia.[14] The Mirena LNG-IUD is FDA approved for the treatment of heavy menstrual bleeding among women who choose to use an IUD for contraception.[15]

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However, a recent systematic review and meta-analysis concluded that because of very low-quality evidence it was difficult to assess the efficacy of the LNG-IUD and progestins for the treatment of fibroids.[16] Tranexamic acid is a nonhormonal option, FDA approved for the treatment of cyclic heavy management of AUB caused by fibroids, and may be an option for women who are near menopause.

## New hormonal treatment adds options for women

Fibroids are the most common pelvic tumor of women. Women with fibroids often present for clinical care due to AUB, pelvic pain, and/or lower abdominal discomfort. For women with symptomatic fibroids it may be difficult to effectively complete employment-related tasks and home responsibilities. In one study, women with symptomatic fibroids reported that their symptoms negatively impacted approximately 20 hours per month of employment-related work and 12 hours per month of home responsibilities, reducing productivity in both settings.[19] Relugolix combination therapy adds another important option for the hormonal treatment of the problems caused by these prevalent and bothersome tumors, improving health and the quality of contributions at work and home. ●


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