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Audience: This activity was designed for OB/GYN physicians, advanced practitioners in women's health and primary care providers who diagnose and treat heavy menstrual bleeding from fibroids.

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FACULTY

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Learning Objectives

At the conclusion of this activity, the participant will be able to:

- Understand mechanism of action of GnRH antagonists
- Appreciate the prevalence and epidemiology of uterine fibroids and heavy menstrual bleeding
- Learners will be able to utilize new or combination of GnRH antagonists with add back therapy for the treatment of heavy menstrual bleeding of fibroids

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CONFLICT OF INTEREST DISCLOSURE

Steven R. Goldstein, MD, CCD, NCMP, FACOG
Advisory Board: Scynexis and Myovant
Consultant: Cook OB/GYN and Cooper Surgical
Recipient of Equipment Loan: GE Ultrasound

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Advisory Board: Cooper Surgical and Myovant,
Investigator: Acessa Gynesonics, Microcube, Bayer, Philips and AEGEA

All of the relevant financial relationships for these faculty have been mitigated by peer review completed by peers with no relevant financial relationships to disclose.

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SUPPLEMENT TO
OBG MANAGEMENT

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Non-Surgical Treatment of Heavy Menstrual Bleeding From Fibroids: A New Paradigm

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Introduction

Leiomyomas, most often referred to as uterine fibroids, are the most common benign pelvic tumors. It appears they originate from clonal expansion of a single myometrial cell.[1] They are hormonally responsive and thus are not seen prior to menarche, with some diminution in size in the menopause.[2] By age 50, approximately 70% of Caucasian women and 80% of Black women will have uterine fibroids.[3] While often asymptomatic and incidental, 25% to 50% of women will experience symptoms, especially heavy menstrual bleeding, iron deficiency with or without anemia, painful pressure symptoms, increased urinary frequency, and reproductive issues.[4] Many women seem to be unaware of their fibroids and their impact on their health. In fact, evidence suggests a woman does not seek treatment for an average of 3.6 years, and 41% see at least 2 healthcare providers before being diagnosed.[5]

Risk factors for fibroids include race, age, hypertension, diet, time since last birth, family history, and being premenopausal.[6] Fibroids and their related symptoms have been shown to have a negative impact on physical and social activities, quality of life, and work productivity.[5] The economic burden is substantial with an estimated annual direct and indirect cost related to uterine fibroids in the United States as high as 34.4 billion dollars.[7] Until recently, the most common first-line treatment has been hormonal contraceptives, although these are "off label." For many years, injectable gonadotropin-releasing hormone (GnRH) agonists like leuprolide acetate have often been employed. Interestingly, leuprolide acetate's actual approval indication is "for concomitant use with iron therapy for hematologic improvement of patients with anemia caused by uterine leiomyomata."[8]

The GnRH antagonist elagolix, administered with estradiol and norethindrone acetate, reduces heavy menstrual bleeding in women with uterine fibroids[9] and is approved for the treatment

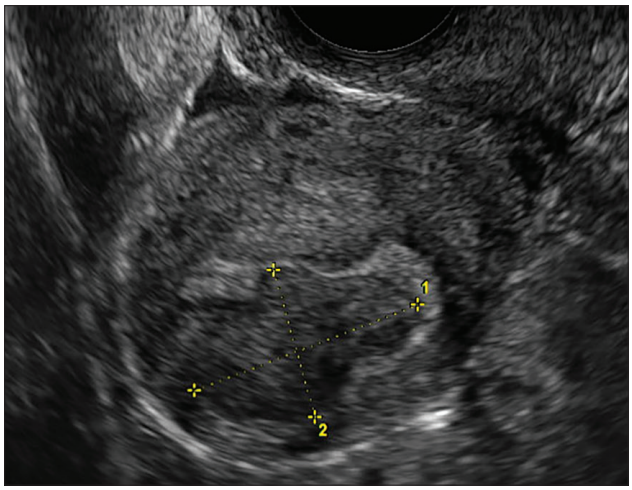

FIGURE 1 Transvaginal sonogram showing an intramural/subserosal fibroid with history of heavy menstrual bleeding. This is an excellent candidate for newer GnRH antagonist – combination hormonal add back oral therapy.

of uterine fibroids for 24 months.[10] However, elagolix involves twice-daily administration because of its short half-life,[11] and its use has been associated with a loss of bone mineral density at 1 year as well as adverse effects on blood pressure and levels of lipids and liver enzymes.[10]

A More Recent GnRH Antagonist With Add-Back Therapy

Al-Hendy and colleagues[12] reported results from the LIBERTY 1 and LIBERTY 2 phase 3 clinical trials evaluating once-daily relugolix combination therapy for heavy menstrual bleeding associated with fibroids. These parallel, double-blinded, placebo-controlled trials together enrolled 770 women with an average age of 42 years from 80 sites across Africa, Europe, North America, and South America. The mean body mass index was similar in both cohorts at 32kg/m^2 and the baseline menstrual blood loss was 245.4 (± 186.4) mL for the relugolix combined therapy and 207.4 (± 114.3) mL for the placebo group. Additionally, and importantly, over 50% of the participants were African American. This is especially important because uterine fibroids are more common in this group.[3]

Inclusion for heavy menstrual bleeding was defined as 80 mL or greater per cycle for 2 consecutive cycles or 160 mL or greater during 1 cycle. All blood loss was measured by the alkaline hematin method for direct measurement of the volume of menstrual blood loss. Participants were blindly randomized in a 1:1:1 ratio to receive either 1) 24 weeks of placebo, 2) relugolix combination therapy (relugolix 40 mg with 1 mg estradiol and 0.5 mg norethindrone acetate) for 24 weeks, or 3) relugolix monotherapy for 12 weeks followed by relugolix combination therapy for 12 weeks.[12]

This trial, similar to the elagolix phase 3 trial, defined a primary efficacy endpoint as the percentage of participants with both a volume of menstrual blood loss of <80 mL and a reduction of at least 50% from the baseline volume of menstrual blood loss. Unique to this trial, however, was the inclusion of secondary endpoints that specifically assessed amenorrhea, volume of menstrual blood loss, distress from bleeding and pelvic discomfort, anemia, pain, uterine volume, and largest fibroid volume.

In the LIBERTY 1 and LIBERTY 2 trials, 73% and 71% of patients in the relugolix combination groups, respectively, achieved the primary endpoint compared to 19% and 15% in the placebo groups ($P < .001$). In regard to the secondary endpoints, relugolix was superior to placebo in both trials for 6 of the 7 endpoints (**Table 1**).

The rate of adverse events between groups was similar with 66% in the placebo group, 62% in the relugolix combination therapy group, and 73% in the delayed relugolix combination group. Hot flashes were the most commonly reported event in 8%, 11%, and 36% of patients, respectively. Changes in bone mineral density were similar in the placebo and combination therapy groups for both trials, while there was a significant decrease observed in the delayed group. Serious adverse events were very infrequent.

Clinical Relevance

When evaluating the spectrum of fibroid treatment options, the approval of medications with a primary indication for the treatment of fibroids is quite exciting. This is even more pronounced since almost all other first-line treatment options, such as oral contraceptives, do not have an indication or evidence for their efficacy in the treatment of fibroids. Historically, depot leuprolide was the only other medication that had an indication for fibroid treatment. However, it is indicated for a maximum of 6 months of use primarily for preoperative management of fibroids or bridging to menopause, due to the significant hypoestrogenic state induced. In the relugolix combination trial, the maintenance of bone density and vasomotor symptoms were not increased over placebo. This was not the case in the elagolix combination trial, in which hot flashes were significantly increased compared to placebo.[13] More recently, among patients treated with relugolix combination therapy through 52 weeks, sustained improvement in heavy menstrual bleeding was observed in 87.7%, with 70.6% of patients achieving amenorrhea. At week 52, 59.0% of patients with anemia at baseline had improvements in hemoglobin concentration of >2 g/dL. Distress due to uterine leiomyoma-associated symptoms was reduced. Sustained reductions in uterine and uterine leiomyoma volume were observed. Bone mineral density was preserved through week 52.[14]

Another important finding from this study was improvement in pain symptoms. While abnormal bleed-

TABLE 1 Efficacy of secondary outcomes with relugolix combination versus placebo

	LIBERTY 1 Trial			LIBERTY 2 Trial		
	Placebo (N = 127)	Relugolix Combination Therapy (N = 128)	*P* value vs placebo	Placebo (N = 129)	Relugolix Combination Therapy (N = 125)	*P* value vs placebo
Amenorrhea over last 35 days of treatment period	7 (6%)	67 (52%)	<0.001	4 (3%)	63 (50%)	<0.001
Percent change from baseline to week 24 in menstrual blood-loss volume	–23.2±4.6	–84.3±4.7	<0.001	–15.1±5.5	–84.3±5.5	<0.001
Change from baseline to week 24 in Bleeding and Pelvic Discomfort Scale score	–16.1±2.8	–45.0±2.9	<0.001	–18.3±2.9	–51.7±2.9	<0.001
Participants with anemia at baseline and an increase in hemoglobin level of >2 g/dL at week 24	5/23 (22%)	15/30 (50%)	0.04	2/37 (5%)	19/31 (61%)	<0.001
Participants in pain with maximum numerical rating scale score ≤1 over last 35 days of treatment period	7/69 (10%)	25/58 (43%)	<0.001	14/82 (17%)	32/68 (47%)	<0.001
Percent change from baseline to week 24 in volume of primary uterine fibroid	–0.3±5.4	–12.4±5.6	0.09	–7.4±5.9	–17.4±5.9	0.22
Percent change from baseline to week 24 in uterine volume	2.2±3.0	–12.9±3.1	<0.001	–1.5±3.4	–13.8±3.4	<0.001

ing associated with fibroids typically gets most of the attention, pain is a significant and often debilitating part of this disease. In the relugolix combination trial, pain was reported at baseline in approximately 70% of the subjects. In the LIBERTY 1 and LIBERTY 2 trials, the amount of women who achieved the endpoint of minimal to no pain was 65% (95% CI: 55.6%, 73.5%) and 44.6% (95% CI: 32.3%, 7.5%) compared with placebo (19.3% [95% CI: 13.2%, 26.7%], nominal $P = 0.001$, and 21.6% [95% CI: 12.9%, 32.7%], nominal $P = 0.004$, respectively). This means that there is an option to offer treatment to patients who may not be dealing with bleeding issues but with other fibroid-related concerns. This is the first medical option to provide evidence to this effect.

Another major advantage of relugolix combination therapy pertains to dosing, specifically a once-daily oral dosage. When compared to leuprolide, which requires an intramuscular injection, the majority of patients prefer an oral route. The once-daily dosage compared to the twice-daily dosage of different pill formulations is another advantage compared with elagolix combination therapy. Patient compliance is higher in single vs multiple doses per day.

What still remains to be seen is the long-term efficacy of this entire class. The clinical trials only lasted for 24 months, which leaves us with what is the appropriate measure for younger women who complete this course of therapy. In this trial, the mean age was 42, meaning that most of these women had a large amount of time before entering menopause, for which they may still need treatment. Additionally, pregnancy is not recommended during treatment, although the likelihood of pregnancy will probably be decreased due to decreased ovulation. Also, the impact on future fertility after discontinuation has not been studied.

Summary

The GnRH antagonists with add back estrogen/progesterone are promising new additions to the armamentarium of options for treating our patients. As we try to tailor our treatments to best fit each individual patient's needs, a new medical treatment offers us an immediate option that is uterine sparing. Whether it be to completely avoid surgery, delay surgery until a more convenient time, optimize a patient's anemia and uterine size preoperatively, or as a "bridge" to menopause, this therapeutic option will greatly benefit our patients. ●

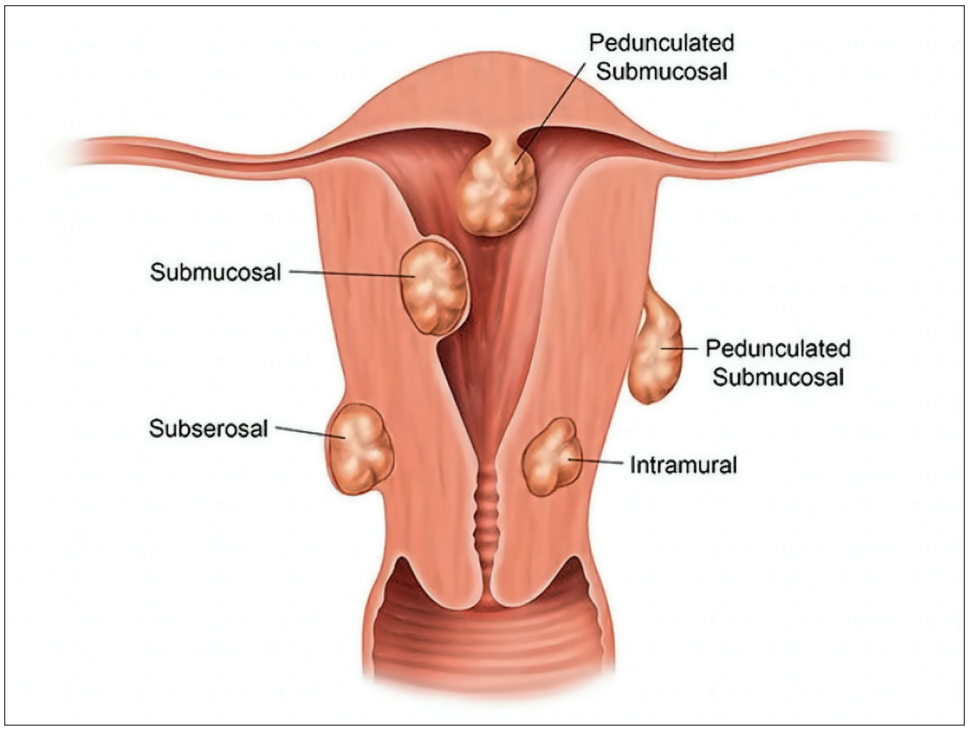

FIGURE 2 Schematic drawing showing various locations of leiomyomas.

REFERENCES

1. Bulun SE. Uterine fibroids. *N Engl J Med*. 2013;369(14):1344-1355.
2. Marsh EE, Bulun SE. Steroid hormones and leiomyomas. *Obstet Gynecol Clin North Am*. 2006;33(1):59-67.
3. Wise LA, Laughlin-Tommaso SK. Epidemiology of uterine fibroids: from menarche to menopause. *Clin Obstet Gynecol*. 2016;59(1):2-24.
4. Bartels CB, Cayton KC, Chuong FS et al. An evidence-based approach to the medical management of fibroids: a systematic review. *Clin Obstet Gynecol*. 2016;59(1):30-52.
5. Borah BJ, Nicholson WK, Bradley L, Stewart EA. The impact of uterine leiomyomas: a national survey of affected women. *Am J Obstet Gynecol*. 2013;209(4): 319.e1-319.e20.
6. Stewart EA, Cookson CL, Gandolfo RA, Schulze-Rath R. Epidemiology of uterine fibroids: a systematic review. *BJOG*. 2017;124(10):1501-1512.
7. Cardozo ER, Clark AD, Banks NK, Henne MB, Stegmann BJ, Segars JH. The estimated annual cost of uterine leiomyomata in the United States. *Am J Obstet Gynecol*. 2012;206(3):211.e1 211.e2119.
8. Lupron Depot [package insert]. North Chicago, IL: AbbVie Inc., 2018.
9. Schlaff WD, Ackerman RT, Al-Hendy A, et al. Elagolix for heavy menstrual bleeding in women with uterine fibroids. *N Engl J Med* 2020; 382(4):328-340.
10. Food and Drug Administration. Oriahnn (elagolix, estradiol, and norethindrone acetate capsules; elagolix capsules) prescribing information. 2020. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/213388s000lbl.pdf
11. Ng J, Chwalisz K, Carter DC, Klein CE. Dose-dependent suppression of gonadotropins and ovarian hormones by elagolix in healthy premenopausal women. *J Clin Endocrinol Metab.* 2017; 102(5):1683–91.
12. Al-Hendy A, Lukes AS, Poindexter AN 3rd, et al. Treatment of uterine fibroid symptoms with relugolix combination therapy. *N Engl J Med*. 2021;384(7):630-642.
13. Schlaff WD, Ackerman RT, Al-Hendy A et al. Elagolix for heavy menstrual bleeding in women with uterine fibroids. *N Engl J Med*. 2020;382(4):328-340.
14. Al-Hendy A, Lukes AS, Poindexter AN 3rd, et al. Long-term relugolix combination therapy for symptomatic uterine leiomyomas. *Obstet Gynecol*. 2022;140(6):920-930.