

New hormonal medical treatment is an important advance for AUB caused by uterine fibroids

Women with fibroids causing symptomatic abnormal uterine bleeding who choose to avoid a therapeutic procedure have a new hormonal treatment option



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Uterine leiomyomata (fibroids) are the most common pelvic tumor diagnosed in women.¹ Women with symptomatic fibroids often report abnormal uterine bleeding (AUB) and pelvic cramping, fullness, or pain. Fibroids also may cause frequency of urination and contribute to fertility and pregnancy problems. Treatment options for the AUB caused by fibroids include, but are not limited to, hysterectomy, myomectomy, uterine artery embolization, endometrial ablation, insertion of a levonorgestrel intra-uterine device, focused ultrasound surgery, radiofrequency ablation, leuprolide acetate, and elagolix plus low-dose hormone add-back (Oria; AbbVie, North Chicago, Illinois).¹ Oria is the most recent addition to our treatment armamentarium for fibroids and represents the first US Food and Drug Administration (FDA)-approved long-term hormonal option for AUB caused by fibroids.

Gene dysregulation contributes to fibroid development

Most uterine fibroids are clonal tumors, which develop following a somatic mutation in a precursor uterine myocyte. The somatic mutation causes gene dysregulation that stimulates cell growth resulting in a benign tumor mass. The majority of fibroids contain a mutation in one of the following 6 genes: *mediator complex subunit 12 (MED12)*, *high mobility group AT-hook (HMGA2 or HMGA1)*, *RAD51B*, *fumarate hydratase (FH)*, *collagen type IV, alpha 5 chain (COL4A5)*, or *collagen type IV alpha 6 chain (COL4A6)*.²

Gene dysregulation in fibroids may arise following chromothripsis of the uterine myocyte genome

Chromothripsis is a catastrophic intracellular genetic event in which one or more chromosomes are broken and reassemble in a new nucleic

acid sequence, producing a derivative chromosome that contains complex genetic rearrangements.³ Chromothripsis is believed to occur frequently in uterine myocytes. It is unknown why uterine myocytes are susceptible to chromothripsis,³ or why a catastrophic intracellular event such as chromothripsis results in preferential mutations in the 6 genes that are associated with myoma formation.

Estrogen and progesterone influence fibroid size and cell activity

Although uterine fibroids are clonal tumors containing broken genes, they are also exquisitely responsive to estradiol and progesterone. Estradiol and progesterone play an important role in regulating fibroid size and function.⁴ Estrogen stimulates uterine fibroids to increase in size. In a hypoestrogenic state, uterine fibroids

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decrease in size. In addition, a hypoestrogenic state results in an atrophic endometrium and thereby reduces AUB. For women with uterine fibroids and AUB, a reversible hypoestrogenic state can be induced either with a parenteral GnRH-agonist analogue (leuprolide) or an oral GnRH-antagonist (elagolix). Both leuprolide and elagolix are approved for the treatment of uterine fibroids (see below).

Surprisingly, progesterone stimulates cell division in normal uterine myocytes and fibroid cells.⁵ In the luteal phase of the menstrual cycle, uterine myocyte mitoses are more frequent than in the follicular phase. In addition, synthetic progestins appear to maintain fibroid size in a hypoestrogenic environment. In one randomized trial, women with uterine fibroids treated with leuprolide acetate plus a placebo pill for 24 weeks had a 51% reduction in uterine volume as measured by ultrasound.⁶ Women with uterine fibroids treated with leuprolide acetate plus the synthetic progestin, oral medroxyprogesterone acetate 20 mg daily, had only a 15% reduction in uterine volume.⁶ This finding suggests that synthetic progestins partially block the decrease in uterine volume that occurs in a hypoestrogenic state.

Further evidence that progesterone plays a role in fibroid biology is the observation that treatment of women with uterine fibroids with the antiprogestin ulipristal decreases fibroid size and reduces AUB.⁷⁻⁹ Ulipristal was approved for the treatment of fibroids in many countries but not the United States. Reports of severe, life-threatening liver injury—some necessitating liver transplantation—among women using ulipristal prompted the European Medicines Agency (EMA) in 2020 to recommend that women **stop taking ulipristal**. In addition, the EMA recommended

that **no woman should initiate ulipristal treatment at this time**.¹⁰

Leuprolide acetate

Leuprolide acetate is a peptide GnRH-agonist analogue. Initiation of leuprolide treatment stimulates gonadotropin release, but with chronic administration pituitary secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) decreases, resulting in reduced ovarian follicular activity, anovulation, and low serum concentration of estradiol and progesterone. Leuprolide treatment concomitant with iron therapy is approved by the FDA for improving red blood cell volume prior to surgery in women with fibroids, AUB, and anemia.¹¹ Among women with fibroids, AUB, and anemia, after 12 weeks of treatment, the hemoglobin concentration was ≥ 12 g/dL in 79% treated with leuprolide plus iron and 56% treated with iron alone.¹¹ The FDA recommends limiting preoperative leuprolide treatment to no more than 3 months. The approved leuprolide regimens are a maximum of 3 monthly injections of leuprolide 3.75 mg or a single injection of leuprolide 11.25 mg. Leuprolide treatment prior to hysterectomy surgery for uterine fibroids usually will result in a decrease in uterine size and may facilitate vaginal hysterectomy.

Elagolix plus estradiol plus norethindrone acetate (OriaHnn)

GnRH analogues cause a hypoestrogenic state resulting in adverse effects, including moderate to severe hot flashes and a reduction in bone mineral density. One approach to reducing the unwanted effects of hot flashes and decreased bone density

is to combine a GnRH analogue with low-dose steroid hormone add-back therapy. Combining a GnRH analogue with low-dose steroid hormone add-back permits long-term treatment of AUB caused by fibroids, with few hot flashes and a minimal decrease in bone mineral density. The FDA recently has approved the combination of elagolix plus low-dose estradiol and norethindrone acetate (OriaHnn) for the long-term treatment of AUB caused by fibroids.

Elagolix is a nonpeptide oral GnRH antagonist that reduces pituitary secretion of LH and FSH, resulting in a decrease in ovarian follicular activity, anovulation, and low serum concentration of estradiol and progesterone. Unlike leuprolide, which causes an initial increase in LH and FSH secretion, the initiation of elagolix treatment causes an immediate and sustained reduction in LH and FSH secretion. Combining elagolix with a low dose of estradiol and norethindrone acetate reduces the side effects of hot flashes and decreased bone density. Clinical trials have reported that the combination of elagolix (300 mg) twice daily plus estradiol (1 mg) and norethindrone acetate (0.5 mg) once daily is an effective long-term treatment of AUB caused by uterine fibroids.

To study the efficacy of elagolix (alone or with estrogen-progestin add-back therapy) for the treatment of AUB caused by uterine fibroids, two identical trials were performed,¹² in which 790 women participated. The participants had a mean age of 42 years and were documented to have heavy menstrual bleeding (>80 mL blood loss per cycle) and ultrasound-diagnosed uterine fibroids. The participants were randomized to one of 3 groups:

- elagolix (300 mg twice daily) plus low-dose steroid add-back

Fibroids: Impact of age and race

Black women are more likely to develop fibroids and experience more severe fibroid symptoms. Obstetrician-gynecologists are experts in the diagnosis and treatment of fibroids. We play a key role in partnering with Black women to reduce fibroid disease burden.

Factors that increase the risk of developing fibroids include: increasing age, Black race, nulliparity, early menarche (<10 years of age), obesity, and consumption of red meat.¹ The Nurses Health Study II is the largest prospective study of the factors that influence fibroid development.² A total of 95,061 premenopausal nurses aged 25 to 44 years were followed from September 1989 through May 1993. Review of a sample of medical records demonstrated that the nurses participating in the study were reliable reporters of whether or not they had been diagnosed with fibroids. Based on a report of an ultrasound or hysterectomy diagnosis, the incidence rate for fibroids increased with age. Incidence rate per 1,000 women-years was 4.3 (age 25 to 29 years), 9.0 (30 to 34 years), 14.7 (age 35 to 39 years), and 22.5 (40 to 44 years). Compared with White race, Black race (but not Hispanic ethnicity or Asian race) was associated with an increased incidence of fibroids. Incidence rate per 1,000 women-years was 12.5 (White race), 37.9 (Black race), 14.5 (Hispanic ethnicity), and 10.4 (Asian race). The risk of developing fibroids was 3.25 times (95% CI, 2.71 to 3.88) greater among Black compared with White women after controlling for body mass index, age at first birth, years since last birth, history of infertility, age at first oral contraceptive use, marital status, and current alcohol use.²

Other epidemiology studies also report an increased incidence of fibroids among Black women.^{3,4} The size of the uterus, the size and number of fibroids, and the severity of fibroid symptoms are greater among Black versus White women.^{5,6} The molecular factors that increase fibroid incidence among Black women are unknown. Given the burden of fibroid disease among Black women, obstetrician-gynecologists are best positioned to ensure early diagnosis and to develop an effective follow-up and treatment plan for affected women.

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(1 mg estradiol and 0.5 mg norethindrone acetate once daily),

- elagolix 300 mg twice daily with no steroid add-back (elagolix alone), or
- placebo for 6 months.¹²

Menstrual blood loss was quantified using the alkaline hematin method on collected sanitary products. The primary endpoint was menstrual blood loss <80 mL per cycle as well as a ≥50% reduction in quantified blood loss from baseline during the final month of treatment. At 6 months, the percentage of women achieving the primary endpoint in the first trial was 84% (elagolix alone), 69% (elagolix plus add-back),

and 9% (placebo). Mean changes from baseline in lumbar spine bone density were -2.95% (elagolix alone), -0.76% (elagolix plus add-back), and -0.21% (placebo). The percentage of women reporting hot flashes was 64% in the elagolix group, 20% in the elagolix plus low-dose steroid add-back group, and 9% in the placebo group. Results were similar in the second trial.¹²

The initial trials were extended to 12 months with two groups: elagolix 300 mg twice daily plus low-dose hormone add-back with 1 mg estradiol and 0.5 mg norethindrone acetate once daily (n = 218) or elagolix 300 mg twice daily (elagolix alone)

(n = 98).¹³ Following 12 months of treatment, heavy menstrual bleeding was controlled in 88% and 89% of women treated with elagolix plus add-back and elagolix alone, respectively. Amenorrhea was reported by 65% of the women in the elagolix plus add-back group. Compared with baseline bone density, at the end of 12 months of treatment, bone mineral density in the lumbar spine was reduced by -1.5% and -4.8% in the women treated with elagolix plus add-back and elagolix alone, respectively. Compared with baseline bone density, at 1 year following **completion** of treatment, bone mineral density in the lumbar spine was reduced

by -0.6% and -2.0% in the women treated with elagolix plus add-back and elagolix alone, respectively. Similar trends were observed in total hip and femoral neck bone density. During treatment with elagolix plus add-back, adverse effects were modest, including hot flushes (6%), night sweats (3.2%), headache (5.5%), and nausea (4.1%). Two women developed liver transaminase levels >3 times the upper limit of normal, resulting in one woman discontinuing treatment.¹³

Contraindications to Oriahnn include known allergies to the components of the medication (including the yellow dye tartrazine); high risk of arterial, venous thrombotic or thromboembolic disorders; pregnancy; known osteoporosis; current breast cancer or other hormonally-sensitive malignancies; known liver disease; and concurrent use of organic anion transporting polypeptide 1B1 inhibitors, which includes many HIV antiviral medications.¹⁴ Undiagnosed AUB is a contraindication, and all women prescribed Oriahnn should have endometrial sampling before initiating treatment. Oriahnn should not be used for more than 24 months due to the risk of irreversible bone loss.¹⁴ Systemic estrogen and progestin combinations, a component

of Oriahnn, increases the risk for pulmonary embolism, deep vein thrombosis, stroke, and myocardial infarction, especially in women at increased risk for these events (such as women >35 years who smoke cigarettes and women with uncontrolled hypertension).¹⁴ In two studies there was a higher incidence of depression, depressed mood, and/or tearfulness in women taking Oriahnn (3%) compared with those taking a placebo (1%).¹⁴ The FDA recommends promptly evaluating women with depressive symptoms to determine the risks of initiating and continuing Oriahnn therapy. In two studies there was a higher risk of reported alopecia among women taking Oriahnn (3.5%) compared with placebo (1%).¹⁴

It should be noted that elagolix is approved for the treatment of pelvic pain caused by endometriosis at a dose of 150 mg daily for 24 months or 200 mg twice daily for 6 months. The elagolix dose for the treatment of AUB caused by fibroids is 300 mg twice daily for up to 24 months, necessitating the addition of low-dose estradiol-norethindrone add-back to reduce the frequency and severity of hot flashes and minimize the loss of bone density. Norethindrone acetate also protects the endometrium from the stimulatory

effect of estradiol, reducing the risk of developing endometrial hyperplasia and cancer. Oriahnn is formulated as two different capsules. A yellow and white capsule contains elagolix 300 mg plus estradiol 1 mg and norethindrone acetate 0.5 mg to be taken in the morning, and a blue and white capsule contains elagolix 300 mg to be taken in the evening.

AUB caused by fibroids is a common problem in gyn practice

There are many procedural interventions that are effective in reducing AUB caused by fibroids. However, prior to the approval of Oriahnn there were no hormonal medications that were FDA approved for the long-term treatment of AUB caused by fibroids. Hence, Oriahnn represents an important advance in the hormonal treatment of AUB caused by fibroids and expands the treatment options available to our patients. ●



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