

# UPDATE Abnormal uterine bleeding



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Expert perspectives on a new cryotherapy device for endometrial ablation, the importance of quality of life issues in women with fibroids, and keeping up with randomized trials of elagolix with hormonal add-back therapy

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**A**bnormal uterine bleeding (AUB) continues to be a top-10 reason why women present for gynecologic care, which makes keeping up with clinical therapies important. Over the past year, we have learned a tremendous amount about elagolix with hormonal add-back therapy for the treatment of bleeding associated with uterine fibroids. In this Update, we provide an overview from 3 randomized clinical trials on the recent US Food and Drug Administration (FDA)-approved drug, elagolix with hormonal add-back therapy (approved

May 29, 2020). In addition, we review the data on the Cerene cryotherapy device (Channel Medsystems), as one might rightly ask, do we need another endometrial ablation device? We will address that question, as this device has some unique features that gynecologists should be aware of. Last, we review a study on the importance of considering quality of life in patients with uterine fibroids, which provides sobering information on the psychosocial aspects of uterine fibroids that all clinicians who care for such patients should be aware of.

## Endometrial ablation with a new cryotherapy device: Is less more?



Curlin HL, Cintron LC, Anderson TL. A prospective, multicenter, clinical trial evaluating the safety and effectiveness of the Cerene device to treat heavy menstrual bleeding. *J Minim Invasive Gynecol.* 2021;28:899-908.

**T**he phrase “less is more,” in the world of architecture and design, is often associated with Ludwig Mies van der Rohe (1886–1969). One could argue that this principle is one key advantage with the addition

of yet another non-resectoscopic endometrial ablation device. The Cerene cryotherapy device, FDA approved in 2019, is presented as a simple, disposable device for in-office use that takes advantage of natural cryoanesthesia and results in less tissue destruction than many other ablation methods.

### Device reduces bleeding and permits greater ability for future evaluation

Recently, Curlin and colleagues conducted a prospective, multicenter clinical trial to evaluate the safety and efficacy of the Cerene device in reducing menstrual blood loss.<sup>1</sup> They followed 230 patients over 12 months and found that 81% (77% with intention-to-treat analysis) met the primary end point of a pictorial blood loss assessment chart (PBLAC) score of 75 or lower. Clinically, this translated to 44% of patients experiencing light bleeding; 27%, eumenorrhea; and 10%, amenorrhea. This is clearly “less” in terms of the rate of amenorrhea in most endometrial ablation studies. However, this also may translate into “more” ability to evaluate the endometrial cavity in the future, as 97% of the patients were able to undergo hysteroscopy at the 12-month mark and, of those, 93% were able to have the entire endometrial cavity assessed.

Further, of 97 patients who had a tubal sterilization, none had symptoms or evidence of postablation tubal sterilization syndrome. Three patients were unable to undergo hysteroscopy due to pain intolerance (2) or cervical stenosis (1). This is important because some gynecologists have expressed concern over intrauterine synechiae, which may result in scarring and associated future difficulty in assessing the endometrium for possible cancer.

### Details about the device

The Cerene device is a single use, disposable device that uses cryothermal energy from nitrous oxide that results in a liquid-to-gas phase change within a polyurethane

### WHAT THIS EVIDENCE MEANS FOR PRACTICE

The new Cerene cryotherapy endometrial ablation method meets the FDA's target for reduction of menstrual blood loss, but it has a slightly lower amenorrhea rate than other devices. Its most significant features are the potential for improved analgesia for in-office use and the possibility that there may be less scarring of the endometrial cavity for future assessment if needed.

balloon (resulting in a temperature of -86°C) and delivered through a 6-mm sheath. It may be used in uterine cavities that measure between 2.5 and 6.5 cm in length, corresponding to approximately 10 cm in a uterine sound measurement. Treatment time is 2.5 minutes of nitrous oxide flow.

As mentioned, another benefit claimed is that the Cerene device's cryoanalgesia properties enable the procedure to be more tolerated in the office setting. Of the 230 patients studied in the Curlin trial, no procedures were performed under general anesthesia.<sup>1</sup> Medications used included paracervical block (PCB) only (8%), PCB plus nonsteroidal anti-inflammatory drugs (19.8%), PCB plus oral narcotics/anxiolytics (69%), and PCB plus intravenous sedation (2.9%), showing that this device is ideally suited for in-office use.

The rate of serious adverse events was 2.5% (7 total events in 6 patients within 12 months). All serious adverse events were reviewed by a Clinical Events Committee and none were deemed to be device-related events.

### Long-term outcomes remain to be seen

For physicians and patients who worry about the ability to access the endometrial cavity in the future, less may be more. It will be interesting to see what the long-term outcomes show with use of the Cerene cryotherapy device, and whether a lower amenorrhea rate will translate into a higher repeat intervention rate or not. Of course, not all are minimalists. As the architect Robert Venturi (1925–2018) was quoted as saying, “Less is a bore.”

### FAST TRACK

*Of 230 patients treated with the Cerene device, 81% met the primary end point of a PBLAC score of 75 or lower, and 97% were able to undergo hysteroscopy at 12 months*

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## QoL assessment in women with fibroids is useful in evaluating treatment success

Go VAA, Thomas MC, Singh B, et al. A systematic review of the psychosocial impact of fibroids before and after treatment. *Am J Obstet Gynecol.* 2020;223:674-708.e8.

In many studies that assess AUB, the primary emphasis generally is placed on quantitation of menstrual bleeding by using PBLAC and alkaline hematin scores. In a systematic review, Go and colleagues argue the case for the importance of measuring the psychosocial impact of abnormal bleeding, emphasizing the concerning finding that many women with fibroids report lower vitality and lower social function scores than women with breast cancer.<sup>2</sup>

### Fibroids associated with inconvenience—and anxiety

The authors analyzed and reviewed 18 randomized trials and 39 observational studies after screening 3,625 records from electronic

database searches, with the goal to include only studies with validated quality of life (QoL) questionnaires that were administered both before and after treatment. A highlighted aspect of the reviewed studies was that “control” and “concern” subscales were most affected by fibroids, noting the inconvenience and anxiety that are related to the unpredictable onset and intensity of menses and the feeling of loss of control over one’s health and future.

This systematic review is important because although previous research has shown that fibroids significantly affect QoL, the psychosocial burden of fibroid symptoms had not been compared across different QoL instruments for both disease-specific and general validated health subscales.

### Disability levels with fibroids are similar to those with other chronic diseases

Go and colleagues further reported that uterine fibroids have considerable psychosocial impact and lead to poor overall QoL physically and emotionally, with diminished sexual function and increased urinary or defecatory issues. Women with fibroids experienced a level of disability that was similar to that seen in other chronic diseases, and their vitality scores were lower than those associated with heart disease, diabetes, and as mentioned, breast cancer.

The authors concluded that “although objective clinical measures are important to establish a comprehensive understanding of health status, patient reported QoL outcomes play a critical role in evaluating success of a therapy.” They suggested that a larger emphasis on patient-centered care may help to mitigate the psychosocial effects of fibroids.

### FAST TRACK

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### WHAT THIS EVIDENCE MEANS FOR PRACTICE

The study by Go and colleagues highlights the significant psychosocial aspects of the heavy menstrual bleeding associated with fibroids, and the authors found that many women with fibroids score in the range of those with other significant diseases, such as breast cancer and diabetes.

We have noted the trend of including QoL in research, and Go and colleagues make an excellent and compelling argument for this trend using quantitative analysis. It is important to consider this not only in our design of future research but also, and perhaps more importantly, in our clinical care of women as we try to better understand what they are experiencing.

# What have we learned over the past year about elagolix for uterine fibroids?



Schlaff WD, Ackerman RT, Al-Hendy A, et al. Elagolix for heavy menstrual bleeding in women with uterine fibroids. *N Engl J Med.* 2020;382:328-340.

Simon JA, Al-Hendy A, Archer DF, et al. Elagolix treatment for up to 12 months in women with heavy menstrual bleeding and uterine leiomyomas. *Obstet Gynecol.* 2020;135:1313-1326.

Al-Hendy A, Bradley L, Owens CD, et al. Predictors of response for elagolix with add-back therapy in women with heavy menstrual bleeding associated with uterine fibroids. *Am J Obstet Gynecol.* 2021;224-72.e1-72.e50.

Data from the Elaris UF-1 and UF-2 6-month, phase 3 trials<sup>3</sup> and the results of the Elaris UF-EXTEND trial with a 6-month extension (totaling 12 months of use)<sup>4</sup> were published in 2020, and the 12-month results were discussed in OBG MANAGEMENT (2020;32[7]:35, 39-40). An additional data analysis from the same researchers assessed the effect of elagolix with hormonal add-back therapy in a number of patient subgroups.<sup>5</sup> These 3 publications have added to our knowledge of this therapy, and it is worth reviewing them in this context.

## Design of the elagolix plus hormonal add-back therapy trials

The initial UF-1 and UF-2 trials were 2 identical, double-blind, randomized, placebo-controlled, 6-month, phase 3 trials designed to evaluate the safety and efficacy of elagolix and hormonal add-back therapy.<sup>3</sup> UF-1 was conducted at 76 sites in the United States from December 2015 through December 2018, whereas UF-2 was conducted at 77 sites in the United States and Canada from February 2016 through January 2019; the

trials were registered separately. Both trials had a 2:1:1 randomization of elagolix (300 mg twice daily) with hormonal add-back therapy (estradiol 1 mg and norethindrone acetate 0.5 mg daily), elagolix alone (300 mg twice daily), or placebo.

In the 6-month studies, the primary end point was both menstrual blood loss of less than 80 mL and at least a 50% reduction of menstrual blood loss as measured by the alkaline hematin method.<sup>3</sup> Among several secondary end points was the assessment of QoL using the Uterine Fibroid Symptom QoL questionnaire (UFS-QoL).

**Trial results.** In UF-1, 68.5% of 206 women, and in UF-2, 76.5% of 189 women, respectively, taking elagolix with add-back therapy met the primary objective. Among women taking elagolix alone, in UF-1, 84.1% of 104 women, and in UF-2, 77% of 95 women, respectively, met criteria. There was improvement in UFS-QoL scores in women receiving elagolix plus add-back therapy with a reduction of symptom severity of -33.2 in UF-1 and -41.4 in UF-2, as compared with the placebo-

## WHAT THIS EVIDENCE MEANS FOR PRACTICE

Elagolix plus hormonal add-back therapy provides several advantages to fibroid care, including a pill form that, as a gonadotropin-releasing hormone (GnRH) antagonist, provides much quicker action than GnRH agonists. The hormonal add-back feature seems to improve QoL measures and has a favorable reported bleeding reduction rate. It also appears to be reasonably safe. Although the studies reviewed here may have some weaknesses, it helps to have another therapy to offer to women who have blood loss associated with fibroids. Deciding on the drug's optimal clinical use has not been fully explored, as it may be a short-term solution to a long-term problem and may not be ideal for all patients with fibroids. Elagolix and hormonal add-back therapy may be advantageous for patients who need to stop bleeding quickly and are trying to decide about their reproductive plans, for patients close to menopause who need a therapy to bridge this gap, and for patients trying to obtain relief between pregnancies.

treated groups (-10.3 and -7.7, respectively).

**Adverse effects.** Elagolix was associated with a low incidence of serious adverse effects, and the addition of hormonal add-back therapy attenuated the decreases in bone mineral density observed with elagolix alone. In both UF-1 and UF-2 trials, bone mineral density did not differ significantly in the groups of women who received elagolix with hormonal add-back therapy versus placebo.

### The extension trial results

Of note, in the 12-month study (6-month extension), the authors reported that 87.9% of the women taking elagolix with hormonal add-back therapy met the primary objective.<sup>4</sup> Among the women taking elagolix alone, 89.4% met the primary objective.

In a review of the AbbVie-funded extension study, the editorial comments in the *Obstetrical and Gynecological Survey* expressed concern over the high proportion of data loss, comparing the number of patients joining the extended trial, patients who completed an additional 6 months of treatment, and patients who completed the posttreatment follow-up period of “up to 12 months.”<sup>6</sup> Approximately one-third of patients were lost between initial enrollment to the subset who completed follow-up. There was concern that “losses of that magnitude pose a serious threat to validity.”<sup>6</sup>

#### References

1. Curlin HL, Cintron LC, Anderson TL. A prospective, multicenter, clinical trial evaluating the safety and effectiveness of the Cerene device to treat heavy menstrual bleeding. *J Minim Invasive Gynecol.* 2021;28:899-908.
2. Go VAA, Thomas MC, Singh B, et al. A systematic review of the psychosocial impact of fibroids before and after treatment. *Am J Obstet Gynecol.* 2020;223:674-708.e8.
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6. *Obstetrical & Gynecological Survey.* 2020;75:545-547.

### Effectiveness in subgroups

Al-Hendy and colleagues analyzed data from the Elaris UF-1 and UF-2 trials to see if the outcomes for elagolix with hormonal add-back therapy demonstrated safety and efficacy in subgroups of patients of varying ages, races and ethnicities, baseline menstrual blood loss, body mass indices, fibroid location, and uterine and fibroid volume.<sup>5</sup>

**Results.** In all subgroups, they found a statistically significant reduction in blood loss in mean menstrual blood loss volume for those treated with elagolix plus hormonal add-back therapy compared with those treated with placebo. As well, in terms of QoL, among all subgroups, the mean change in symptom severity score as well as health-related QoL total score from baseline to month 6 was statistically significantly greater than the mean change in the placebo group.

### The bottom line

Elagolix with hormonal add-back therapy appears to be a safe and effective method to reduce menstrual blood loss associated with uterine fibroids. It also has a favorable effect on QoL and appears to have benefits in subgroups of women of varying ages, races and ethnicities, baseline menstrual blood loss, body mass indices, fibroid location, and uterine and fibroid volume. ●

#### FAST TRACK

An analysis of data from the UF-1 and UF-2 trials in patient subgroups found a statistically significant reduction in blood loss volume for those treated with elagolix plus hormonal add-back therapy compared with those treated with placebo