Elagolix: How far can it go in the world of gynecology?

Since the 1970s, gonadotropin-releasing hormone (GnRH) agonists have been used to suppress the hypothalamic–pituitary–ovarian (HPO) axis via desensitization and downregulation of GnRH receptors. In contrast to this stepwise process that requires a 1- to 2-week period, GnRH antagonists competitively bind to pituitary gonadotrophs to quickly disrupt communication of gonadotropins to the ovary (1). This efficacious suppression of GnRH antagonists has facilitated their use in the treatment of various hormone-dependent medical conditions, such as endometriosis, abnormal uterine bleeding in the setting of leiomyomas, and assisted reproductive technology (ART).

In 2018, the Federal Drug Administration approved the first orally administered GnRH antagonist, elagolix, for the management of moderate to severe pain associated with endometriosis (2). Elagolix expeditiously suppresses the HPO axis within 24 hours of administration in a dose-response relationship. This enables clinicians to tailor dosing in a manner that best fits the patient's needs. One can balance symptoms related to the estrogen-dependent disease while avoiding the downstream effects of the hypoestrogenic state (2). In addition to its flexible dosing, rapid onset of action, and ease of administration, elagolix has a relatively short half-life, which enables serum hormone levels to return to the baseline within 24–48 hours of cessation (3).

In a study published in this month's issue of *Fertility Sterility Reports*, we see how elagolix can advance the clinical practice of controlled ovarian stimulation (COS). Elagolix performed similarly to the traditional GnRH antagonist with respect to inhibiting premature ovulation (4). Seventy-five oocyte donors underwent COS with elagolix initiated at a dose of 200 mg nightly once a 14-mm follicle was noted on transvaginal ultrasound, and elagolix was discontinued 24 hours before GnRH agonist trigger. These donors were compared with the previously cycled oocyte donors who received the injectable GnRH antagonist. Not only was there no significant difference in the peak progesterone (P4) level on the day of trigger but also the average number of total oocytes retrieved and the total number of mature oocytes retrieved were similar between these two groups ($P>.05$). The total cycle length and number of days of stimulation were similar as well ($P>.05$). This study has shown that elagolix can be used safely in COS, while saving the patient added injections and added cost and, most importantly, with similar oocyte yield (4).

Moving forward, the use of an oral GnRH antagonist over an injectable one not only would alleviate pain experienced by the patient but also may alleviate the anxiety associated with the treatment. Patients undergoing COS, especially in the realm of infertility, have already accumulated a significant amount of stress, sadness, and fear before their initial consultation with a reproductive endocrinologist. Lowering the number of injections in COS could improve the patient experience. This could then promote compliance, decrease cycle dropout, and result in a greater number of successful pregnancies. In addition, cost savings with the use of oral medication is another potential benefit of using an oral instead of an injectable GnRH antagonist.

It is important to mention that most of the data obtained on investigation of the potential use of elagolix are limited by its administration in the early follicular phase, before the rise of follicle-stimulating hormone, and before the ovary produces estradiol (E2) and P4 independently (3). Can elagolix suppress the HPO axis to the point of inhibiting ovulation, in the setting of a rising level of serum E2 or when P4 is elevated? A recent study showed that elagolix not only suppressed impending ovulation when administered in the late follicular phase but also quickened luteolysis when administered in the mid-luteal phase (5). These pharmacodynamic properties could facilitate its use not only in cases of random start COS but also in the practice of contraception. The potential contraceptive benefits of elagolix could be twofold: first, its ability to rapidly suppress ovulation and induce luteolysis promotes its use as an emergency contraceptive, similar to levonorgestrel emergency contraception; second, its suppression of the HPO axis could promote its use as a short-acting contraceptive pill. Whether or not elagolix can inhibit endometrial proliferation, thus implantation, remains to be determined.

Furthermore, combination oral contraceptive pills or progestin-only pills are not only used for contraception but also used frequently in ART. Elagolix could potentially replace these traditional means of inhibiting folliculogenesis and quickening luteolysis to assist with the timing of start of COS. A key advancement in the field of ART would be if elagolix could suppress ovulation in the case of supraphysiologic E2 and ultimately replace the injectable GnRH antagonist.

Whether administered in the short- or long-term, cycle days 1–3, or at later points in the menstrual cycle, elagolix has been shown to suppress gonadotropin and ovarian hormones. The opportunities for its use are endless. Elagolix provides valuable opportunities for advancements in gynecology, particularly in the fields of reproductive endocrinology and family planning. More data are needed on its clinical use, specifically related to optimal dosing with respect to different phases in the menstrual cycle and when the E2 levels are supraphysiologic in cases of ART.

Rachel B. Danis, M.D., M.S.
Reproductive Medicine Associates of New York LLP
New York, New York

https://doi.org/10.1016/j.xfre.2023.04.002

REFERENCES

1. Fluker M, Grifo J, Leader A, Levy M, Meldrum D, Muasher SJ, et al. Efficacy and safety of ganirelix acetate versus leuprolide acetate in women undergoing controlled ovarian hyperstimulation. Fertil Steril 2001;75:38–45.
2. Taylor HS, Giudice LC, Lessey BA, Abrao MS, Kotarski J, Archer DF, et al. Treatment of endometriosis-associated pain with elagolix, an oral GnRH antagonist. N Engl J Med 2017;377:28–40.
3. 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;102:1683–91.

4. Boniface C, Schnorr JN, Gray J, Slowey M, McLaughlin J, Cook H, et al. The role of elagolix in the suppression of ovulation in donor oocyte cycles. F S Rep 2023;4:179–82.

5. Danis RB, Sriprasert I, Stanczyk FZ, Paulson RJ, Winer SA, Ho JR. Does timing matter when initiating elagolix in a natural menstrual cycle? F S Rep 2021;2: 308–13.