Does timing matter when initiating elagolix in a natural menstrual cycle?

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Objective: To investigate the efficacy of elagolix when administered at different time points in a menstrual cycle.

Design: Clinical case series.

Setting: Academic reproductive endocrinology center.

Patients: Ovulatory women not desiring pregnancy.

Intervention(s): Six doses of elagolix 200 mg were administered over 4 days, starting at 3 different points in a menstrual cycle: early follicular; late follicular; and midluteal. Serum follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol (E2), and progesterone (P) concentrations were measured at baseline, during elagolix administration, and 1 day after the last dose. Transvaginal ultrasounds were performed to monitor follicle sizes.

Main Outcome Measure(s): Serum FSH, LH, E2, and P.

Result(s): Twelve women, four per group, completed the study. Subjects were 23–42 years of age. Demographics and ovarian reserve parameters were similar among participants. Elagolix suppressed FSH, LH, E2, and P when administered in the early follicular and midluteal phases but had mixed results when administered in the late follicular phase. Two participants demonstrated suppression of all four hormones. One participant ovulated, indicated by an increase in P concentration and development of a corpus luteum. A second participant did not ovulate yet demonstrated an increase in E2 concentration with growth of a dominant follicle. There were no significant differences in median percent change of hormone concentrations across study groups.

Conclusion(s): The results of this study suggest that elagolix can suppress the hypothalamic-pituitary-ovarian axis when initiated at different points in a menstrual cycle. Optimal dosing and treatment window for consistent hormone suppression have yet to be determined.

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Key Words: Elagolix, gonadotropin-releasing hormone (GnRH), GnRH antagonist, hormone suppression, ovulation

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Gonadotropin-releasing hormone (GnRH) and its analogs have been utilized in clinical medicine since their development in early 1970s (1, 2). When administered continuously, GnRH agonists initially produce a flare in secretion of gonadotropin hormones but then inhibit the hypothalamic–pituitary–ovarian (HP0) axis via desensitization and downregulation of GnRH receptors (1, 3). In contrast, GnRH antagonists competitively bind to the GnRH receptor, avoiding the initial flare effect, and prevent gonadotropin secretion from pituitary gonadotrophs (4–6). Gonadotropin-releasing hormone antagonists quickly disrupt communication to the ovary, facilitating their use in the treatment of various hormone-dependent medical conditions, including endometriosis, abnormal uterine bleeding relating to leiomyomas, and assisted reproductive technology (1, 3–5, 7–10).

Gonadotropin-releasing hormone antagonists have historically been administered via subcutaneous injection (4–6). In an effort to avoid an injectable medication and ease patient administration, an oral GnRH antagonist, elagolix, has recently been developed. The Federal Drug Administration (FDA) has approved elagolix for the management of moderate to severe pain associated with endometriosis. Formulations include a low-dose regimen of 150 mg once daily and a high-dose regimen of 200 mg twice daily (BID) (7, 11, 12).
Previous studies have investigated the pharmacokinetics and pharmacodynamics of elagolix in premenopausal women (13–15). The ability of elagolix to suppress follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol (E2), and progesterone (P) has been well documented (11, 13–15). Elagolix demonstrates a dose-response relationship, where BID dosing of at least 200 mg generates a greater level of hormone suppression than 100–200 mg once daily dosing (13–15). In addition, aside from hormone suppression, a recent study demonstrated the ability of elagolix to suppress impending ovulation in a dose-dependent manner (15). These studies typically initiated elagolix shortly after the onset of menses, around cycle days 2–7, and administered elagolix for an extended period of time (13–15). In the early follicular phase, the HPO axis is at its most quiescent period, which provides an opportune time to induce suppression of gonadotropin and ovarian hormones. What is unknown is whether elagolix can efficiently suppress the HPO axis when hormones are already elevated and when elagolix is administered over a short-term period of time. This study aimed to investigate the efficacy of elagolix when administered at brief intervals during various points in a menstrual cycle, when gonadotropin and ovarian hormones are not at their baseline.

MATERIALS AND METHODS
Participants and Study Design
This was a clinical case series conducted at the USC Fertility in Los Angeles, California, USA, approved by the University of Southern California’s Clinical Trials Office and the Institutional Review Board, Study ID HS-10-00674. This study was registered on ClinicalTrials.gov with identifier NCT04060992 and was accepted as an Investigator-Initiated Study by AbbVie Clinical Pharmacology Research Unit (Grayslake, IL, USA). The study was designed with a goal to enroll 12 women. Each consumed elagolix 200 mg PO for a total of six doses over a 4-day period at one of three time points in their menstrual cycle: study group A, early follicular phase (cycle days 1–5); study group B, late follicular phase (cycle days 10–14); study group C, midluteal phase (cycle days 20–24). The goal of this study was to recruit four women per group over a 6-month period. Enrollment began on June 1, 2020, and was completed by December 1, 2020.

Women with ovulatory cycles using nonhormonal contraception were eligible to participate in this study. Before enrollment, past medical and menstrual histories were documented. Women having irregular menses; currently desiring pregnancy; using hormonal therapies; having a known allergy to GnRH antagonist medication; having liver disease, osteoporosis, or uncontrolled mood disorder; or currently using medications metabolized by a cytochrome P350 3A enzyme were excluded. Additionally, women who were within 6 months postpartum or currently lactating or who had received GnRH therapy or Depo-Provera in the last 12 months were not eligible for participation. Ovulatory status was confirmed with a serum midluteal P concentration ≥ 3 ng/mL. Women were divided into the three study groups on the basis of their individual schedules and ability to commit to complete study participation. Human chorionic gonadotropin concentrations were measured in serum or urine on study day 1 to exclude pregnancy before participation.

Once eligibility was confirmed and written informed consent was obtained, participants were given a Participant Diary Card that contained a calendar of when to take elagolix and return for blood work and a transvaginal ultrasound (TVUS). In addition, this form provided participants an opportunity to document side effects, if any. Participants committed to 5 face-to-face study days (study days 1–5). Each study day involved serum measurements of FSH, LH, E2, and P and TVUS to document follicle sizes and growth. A single research investigator (R.B.D.) performed all TVUSs to eliminate interobserver variability. The first tablet of elagolix 200 mg was initiated on the evening of study day 1. Participants continued with BID dosing on study days 2 and 3, followed by a final dose of elagolix 200 mg on the morning of study day 4. Study day 5 was the final day, with participants having consumed their last dose of elagolix approximately 24 h prior, for a final blood draw and TVUS. At this time, participants also returned their Participant Diary Card.

Hormone Measurements
Blood samples were obtained on study days 1–5. On study days 2–3, when elagolix was administered BID, and study day 4, when the final elagolix dose was administered, participants were instructed to arrive 2–4 h after their morning dose. Serum hormone concentrations of FSH, LH, E2, and P were measured using validated electrochemiluminescence immunoassays, cobas e 411 analyzer (Roche Diagnostics, Indianapolis, IN). The assay’s limits of detection for FSH, LH, E2, and P were 0.1 mIU/mL, 0.1 mIU/mL, 5 pg/mL, and 0.05 ng/mL, respectively. Interassay coefficients of variation for all hormone assays were <10%.

Statistical Analysis
Participant demographics and hormone concentration were summarized using descriptive statistics. Baseline demographics and ovarian reserve parameters were presented as median (interquartile range). The Kruskal–Wallis test was used to compare the median across the three study groups. Concentrations of gonadotropin and ovarian hormones during the 5-day study period were presented by menstrual cycle day. Median percent change in hormone concentrations between study day 4 (final elagolix dose) and baseline, as well as study day 5 (24 h after the last elagolix tablet) and baseline, was presented as median percent change and compared using the Kruskal–Wallis test across the three study groups. All statistical analyses were conducted using STATA program (StataCorp. 2019. Stata Statistical Software: Release 16. College Station, TX: StataCorp LLC.). A P value of <.05 was considered as statistically significant.

RESULTS
Participants
Fourteen healthy premenopausal women were recruited to participate in this study. Twelve of these women, four per
group, met eligibility criteria. One participant in study group B missed her elagolix dose and office visit on study day 4, but the remaining participants completed the study in its entirety. Ages of women ranged between 23 and 42 years, and cycle length ranged between 23 and 32 days. None of the women reported endometriosis or leiomyomas. Women had similar demographics and ovarian reserve parameters, both within and across study groups (Table 1). Most women (n = 10, 83.3%) used barrier methods for contraception, while the remaining two women used a copper-containing intrauterine device.

**Hormone Suppression**

Gonadotropin and ovarian hormone concentrations over the 5-day study period are presented in Figure 1. There was immediate suppression of all four hormones after consumption of the first dose of elagolix. After consumption of all six doses (during study days 1–4), FSH concentrations either decreased or minimally changed, and LH concentrations decreased in all 12 participants.

The E2 concentration decreased in all participants, except for one in study group B (Participant #2). In Participant #2, the E2 concentration increased from 185 pg/mL on study day 1 (before the first dose of elagolix) to 217 pg/mL on study day 4 (2–4 h after the final elagolix dose), although the FSH concentration decreased from 7.6 to 3.4 mIU/mL and the LH concentration decreased from 12.7 to 6.1 mIU/mL, while the P concentration remained stable at <0.5 ng/mL. This hormone profile coincided with the growth of a dominant follicle from 14.1 to 17.8 mm.

The P concentrations dropped or remained relatively the same in all but one participant in study group B (Participant #3). After Participant #3 consumed all six doses of elagolix over study days 1–4, the P concentration increased from 0.36 to 1.63 ng/mL, although FSH, LH, and E2 concentrations decreased (Fig. 1). Despite the decrease in E2 concentration over study days 1–4, Participant #3 demonstrated growth of a dominant follicle from 16.1 to 25.4 mm, and by study day 5, 24 h after the last dose of elagolix, corpus luteal cyst measuring 12.0 mm was appreciated. This coincided with an increase in the P concentration to 3.34 ng/mL.

Participant #4, neither of the aforementioned participants, skipped both her elagolix dose and office visit on study day 4.

In general, FSH, LH, E2, and P concentrations decreased in all 12 participants (Table 2). Of the four hormones measured, LH showed the greatest median percent change in concentration across all participants. When examining suppression with respect to timing of elagolix initiation, FSH demonstrated the biggest decrease from baseline when elagolix was initiated in study group B, the late follicular phase (−55.3% [−69.0%, −40.0%]). Luteinizing hormone, E2, and P demonstrated the biggest decrease from baseline when elagolix was initiated in study group C, the midluteal phase (−88.0% [−96.8%, −74.8%], −86.0% [−93.6%, −70.0%], and −88.2% [−93.2%, 25.1%], respectively). The FSH, LH, and E2 concentrations decreased in each study group. With the exception of one participant in study group B, P concentrations in addition decreased across study groups.

Hormone concentrations on study day 5, approximately 24 h after the last elagolix dose, were included to investigate rebound (Table 3). When elagolix was initiated in the early follicular phase (study group A), median percent changes of all four hormones indicated persistent suppression from study day 1. When initiated in the late follicular phase, the E2 concentration had minimal change from baseline (median percent change, 0.6% [−23.5%, 62.4%]), and P concentration increased from baseline (median percent change, 9.0% [−31.0%, 107.6%]). In the midluteal phase, FSH demonstrated a positive change in concentration from baseline (median percent change, 9.0% [−31.0%, 107.6%]).

**Safety**

There were no serious side effects in this study. Only one participant had a side effect from elagolix. This participant noted “slight nausea” on study day 3, which was self-resolving and did not interfere with the participant’s daily activities or desire to continue participation in the study.

**DISCUSSION**

Like GnRH agonists, GnRH antagonists efficiently suppress the HPO axis and have been used for estrogen-dependent diseases, such as endometriosis and abnormal bleeding associated with leiomyomas (7–9). In addition, gonadotropin-releasing hormone antagonists have been used as adjuncts to stimulation protocols in controlled ovarian stimulation (4, 5, 16). In contrast to GnRH agonists,
GnRH antagonists have a faster onset of action and a shorter half-life (13, 14). What makes elagolix unique among the available GnRH antagonists is its oral formulation and availability in multiple doses. Struthers et al. (14) investigated the pharmacokinetics and pharmacodynamics of elagolix in humans over a 7-day interval. Premenopausal women with ovulatory cycles were randomized to placebo or elagolix at various doses. Serum FSH, LH, E2, and P concentrations decreased within the first 24 h of administration (14). Ng et al. (13) conducted a similar study but with more variety in elagolix dosing over a longer period of time (21 vs. 7 days) and investigated the effects of elagolix on P concentrations. All four hormones were suppressed within the first 24 h of elagolix administration and rebounded to baseline within 24–48 h of elagolix cessation (13). More recently, Archer et al. (15) demonstrated a dose-dependent relationship between elagolix and level of hormone suppression, as well as ovulation suppression, when administered in the early follicular phase over a 28–84-day interval. Elagolix proved to not only efficiently suppress the HPO axis but additionally offer flexibility with dosing.

To our knowledge, the current study is the first to demonstrate the response to short-term administration of elagolix when administered at 200 mg BID dosing at three points in a menstrual cycle. When elagolix was administered in the early follicular phase, gonadotropin and ovarian hormones persisted at low concentrations. This held true even 24 h after the last dose.

When initiated in the late follicular phase, elagolix was able to interfere with the increasing preovulatory E2 concentrations in all but one participant (Participant #2). In this participant, E2 concentration increased over the course of...
elagolix administration, which corresponded to the growth of a dominant follicle. Nevertheless, this participant demonstrated a decreased in FSH and LH concentrations and did not have an increase in P concentration (0.23 to 0.34 ng/mL, study days 1–4), thereby demonstrating a potential inhibition of ovulation.

While Participant #3 in the late follicular phase study group exhibited suppression of E2 (225 to 111 pg/mL) while consuming elagolix over study days 1–4, she experienced an increase in P concentration (0.36 to 1.63 ng/mL). This hormone profile coincided with the growth of a dominant follicle from 16.1 to 25.4 mm (study days 1–4), followed by the development of a corpus luteal cyst by study day 5 and an increase in P concentration to 3.63 ng/mL. These findings suggest that the dose of elagolix administered at this particular time in the menstrual cycle failed to suppress ovulation in this participant.

The reasons for why elagolix did not suppress hormones and impede ovulation in all four participants could have been because of subtherapeutic dosing or suboptimal timing of elagolix initiation. Most women in our study were overweight or approaching obesity (Table 1). The body mass index of the aforementioned participant who ovulated was 26.5 kg/m². The elevated body mass index may have hindered the bioavailability of elagolix and its suppressive effects. Additionally, we may have initiated elagolix too late in the follicular phase, at a time where E2 was already acting independently of the HPO axis. In the participant who ovulated, elagolix was initiated on cycle day 16 of a 32-day menstrual cycle. This may have been outside of the optimal treatment window for elagolix to suppress impending ovulation. By the time this participant entered the study, her E2 and LH concentrations were 225 pg/mL and 28.9 mIU/mL, respectively. It is possible that at this point in the participant’s late follicular phase, E2 and LH were already acting independently of GnRH feedback. In this case, this participant could have been passed the threshold for when elagolix could efficiently suppress ovulation.

Optimal timing and dosing of elagolix in the late follicular phase to guarantee consistent hormone suppression and suppression of impending of ovulation have yet to be determined. Archer et al. [15] investigated the ability of elagolix to suppress ovulation, and future studies should include a dose–finding relationship for when elagolix is initiated in the late follicular phase.

Three of the four women who took elagolix during their midluteal phase experienced more rapid onset of menses, which coincided with their decreasing P concentrations. Similar to the findings in study group B, the ability of elagolix to induce luteolysis and provoke an earlier onset of the subsequent menstrual cycle could be dose-dependent and/or timing-dependent.

This pilot study, which investigated the pharmacodynamics of short-term elagolix administration at different time points in a natural menstrual cycle, was limited by its small sample size. Although the larger of the 2 FDA-approved doses for elagolix was used (200 mg BID), not all women demonstrated complete hormone suppression. This poses the question of whether a larger dose of elagolix would have achieved better suppression, particularly in women who are overweight or obese or who have underlying endocrinopathies and whether there is an optimal treatment window

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**TABLE 2**

| Study group A | Study group B | Study group C | Total sample | P value |
|---------------|---------------|---------------|--------------|---------|
| FSH | −25.8 (−45.9, 11.8) | −55.3 (−69.0, −40.0) | −38.0 (−50.1, −13.4) | −40.0 (−55.8, −15.6) | .31 |
| LH | −82.0 (−96.8, −35.6) | −52.0 (−86.9, −50.7) | −88.8 (−96.8, −74.8) | −83.0 (−95.1, −52.0) | .43 |
| E2 | −76.2 (−83.3, −35.7) | −15.5 (−50.7, 17.3) | −86.0 (−93.6, −70.0) | −71.4 (−85.6, −15.5) | .07 |
| P | −36.5 (−76.5, −1.0) | 47.8 (−15.0, 352.8) | −88.2 (−93.2, 25.1) | −15.0 (−91.6, 47.8) | .24 |

Note: E2 = estradiol, FSH = follicle-stimulating hormone, LH = luteinizing hormone, P = progesterone, study group A = early follicular phase, study group B = late follicular phase, study group C = midluteal phase. The percent changes in hormone concentrations across groups in study days 1–4 were not statistically significantly different (P> .05). Data are presented as median (interquartile range) with P value from the Kruskal–Wallis test.

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**TABLE 3**

| Study group A | Study group B | Study group C | Total sample | P value |
|---------------|---------------|---------------|--------------|---------|
| FSH | −7.5 (−21.6, 68.3) | −35.0 (−56.9, 45.7) | 9.0 (−31.0, 107.6) | −14.5 (−36.0, 69.2) | .58 |
| LH | −29.0 (−34.4, −21.1) | −22.8 (−49.1, 46.0) | −45.0 (−74.0, 293.6) | −29.0 (−49.1, −11.3) | .87 |
| E2 | −11.9 (−81.3, 446.1) | 0.6 (−23.5, 62.4) | −86.0 (−92.5, −75.4) | −47.8 (−82.8, 38.3) | .05 |
| P | −32.5 (−67.0, 1.0) | 52.9 (5.9, 450.8) | −88.4 (−95.1, 130.5) | −23.3 (−88.4, 52.9) | .12 |

Note: E2 = estradiol, FSH = follicle-stimulating hormone, LH = luteinizing hormone, P = progesterone, study group A = early follicular phase, study group B = late follicular phase, study group C = midluteal phase. The percent changes in hormone concentrations across groups over the 5-day study period were not statistically significantly different (P> .05). Data are presented as median (interquartile range) with P value from the Kruskal–Wallis test.

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Danis. Effects of elagolix in a menstrual cycle. Fertil Steril Rep 2021.
for elagolix administration. Ng et al. (13) demonstrated maximal FSH suppression when elagolix was administered at 300 and 400 mg BID dosing and maximal LH and E2 suppression when administered at 200 mg BID dosing. However, other research has shown maximal FSH, LH, and E2 suppression at 300 mg BID dosing (15). We chose the 200 mg BID dosing used for the treatment of endometriosis because at the time of this study’s initiation, this was the maximum dose that had been approved by the FDA (7, 8, 11, 12). Before enrollment, women were counseled regarding safety data of this dose already approved for human use (7, 8, 12).

The results of this pilot study demonstrate the potential for differential short-term dose-response efficacy studies on the basis of timing in the menstrual cycle. It is accepted that GnRH has differential pulsatility and amplitude patterns during the early, middle, and late follicular and luteal phases of the menstrual cycle (17). These changes in GnRH secretory patterns may be contributing factors for the varying suppressive effects of elagolix at different phases of the menstrual cycle.

Despite not seeing universal hormone suppression in every participant, we observed a delay in follicular progression in the early follicular phase, an interruption of ovulation in the late follicular phase, and luteolysis in the luteal phase. In light of our findings, elagolix could potentially be used in scheduling controlled ovarian stimulation for assisted reproduction and prevention of ovulation during stimulation or possibly be used as an emergency contraceptive. Clinical applications will require larger dose-response studies as well as studies focusing on cycle timing.

CONCLUSION

In conclusion, elagolix can suppress gonadotropin and ovarian hormones when initiated at various points in a menstrual cycle over a short period of time. Suppression can be seen after a single 200–mg dose. Elagolix can maintain a quiescent hormone profile when administered in the early follicular phase. When initiated in the late follicular phase, elagolix suppresses LH and E2 concentrations in most participants. When administered in the midluteal phase, elagolix can induce luteolysis and shorten the luteal phase. While more data are needed to address the ability of elagolix to suppress ovulation, this study demonstrated the therapeutic potential of elagolix in a wide variety of hormone-dependent conditions.

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