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# Gynecological uses of GnRH antagonists: review article

## Abstract

**Aim:** to review and analyze the use of gonadotropin-releasing hormone (GnRH) antagonists in endometriosis, adenomyosis, non-menstrual pelvic pain, uterine fibroids, prostate cancer, female infertility, and precocious puberty.

**Methods:** the information used to write this manuscript was obtained during a three-month period, between October and May 2022, from specialized literature, written in English and Spanish, related to the use and potential applications of GnRH antagonists in medicine, mainly published during the last five years, using journals found in the most relevant medical digital archives, including PubMed, SciELO, Google Scholar, Cochrane, and Elsevier. Among the keywords used for obtaining this updated information were gonadotropin-releasing hormone (GnRH) antagonists; GnRH receptors (GnRHR); elagolix; relugolix; cetrorelix; linzagolix; hypothalamic-pituitary-gonadal (HPG) axis; endometriosis; adenomyosis; pelvic pain; uterine fibroids; leiomyomas; infertility; precocious puberty; PP; and central PP.

**Results:** GnRH antagonists induce a rapid onset of clinical effects, without the flare-up effect that is seen with agonists, and have immediate therapeutic effects; once treatment concludes, hormonal suppression rapidly ceases, with normalization of gonadal function within a few days, guaranteeing an increase of GnRH concentration, controlling non-menstrual pelvic pain and heavy menstrual bleeding, and serving as part of the treatment of infertility and precocious puberty.

**Conclusion:** even though the aforementioned gynecological pathologies can be treated with the use of multiple drugs, GnRH antagonists have shown to be potential first lines of treatment, as long as their administration protocols are followed correctly.

**Keywords:** adenomyosis; elagolix; endometriosis; infertility; leiomyoma; pelvic pain; precocious puberty.

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## Introduction

The gonadotropin-releasing hormone (GnRH) antagonists are molecules that act as competitive inhibitors of the GnRH receptors (GnRHR) in the adenohypophysis, against endogenous GnRH, and once they bind to this receptor, they cause the immediate suppression of the hypothalamic-pituitary-gonadal (HPG) axis, with a rapid and sustained decline in gonadotropin and sex hormones levels, via downregulation, preventing premature luteinizing hormone (LH) surges.[1–3] These may be used during any time of the follicular phase.[4] The suppression of the HPG axis is dose-related, with lower doses achieving a partial suppression, and higher doses, a full suppression.[3] Antagonists have also shown to behave as agonists in peripheral tissues, an observation that has led to believe that GnRHRs may acquire varying conformations in the different cell types where they are expressed, activating different intracellular signaling pathways, as well.[5] As a matter of fact, the synthesis of the first-generation GnRH antagonists was based on multiple amino acid substitutions, with an intricate structural complexity, and their most deleterious effects, such as anaphylactic reactions and edematogenic effects, were related to histamine release; fortunately, this has changed with the new generation antagonists.[1,3,4]

GnRH antagonists induce a rapid onset of clinical effects, without the flare-up effect that is seen with agonists,[6,7] and have immediate therapeutic effects, - 24 to 72 hours -, and once this treatment concludes, the hormonal suppression rapidly ceases, with normalization of gonadal function within a few days, guaranteeing an increase of GnRH concentration. The use of GnRH antagonists has been destined for the treatment of pathological conditions, such as endometriosis, adenomyosis, uterine fibroids, dysmenorrhea, menorrhagia, female infertility, and precocious puberty (PP).[1–4,8]

The objective of the present manuscript is to review and analyze the use of GnRH antagonists in different gynecological pathologies, including endometriosis, adenomyosis, non-menstrual pelvic pain, uterine fibroids, infertility, and PP, based on their pharmacokinetics, pharmacodynamics, advantages, efficacy, and safety on recently held clinical trials for the aforementioned pathologies, to compartmentalize their effects in one complete and extensive narrative review.

## Methods

The information used to write this manuscript was obtained during a three-month period, between October and May 2022, from specialized literature, written in English and Spanish, related to the use and potential applications of GnRH antagonists in medicine, mainly published during the last five years, using journals found in the most relevant medical digital archives, including PubMed, SciELO, Google Scholar, Cochrane, and Elsevier. Among the keywords used for obtaining this updated information were gonadotropin-releasing hormone (GnRH) antagonists; GnRH receptors (GnRHR); elagolix; relugolix; cetrorelix; linzagolix; hypothalamic-pituitary-gonadal (HPG) axis; endometriosis; adenomyosis; pelvic pain; uterine fibroids; leiomyomas; infertility; precocious puberty; PP; and central PP.

The inclusion criteria were articles published between 2015-2022; published clinical trials about the medical uses of GnRH antagonists;

and articles related to new uses of GnRH antagonists in gynecology. Among the exclusion criteria were articles published more than 10 years ago; manuscripts that were not related to the use of GnRH antagonists; and articles published in non-reliable sources and with questionable outcomes.

A summary of the different studies that were included in the analysis of this manuscript can be seen in Table 1.

## Discussion

### Hypothalamic-pituitary-gonadal axis

The processes of regulation of fertility, normal sexual function, human reproduction, and expression of sexual characteristics are directly dependent on an intricate neuroendocrine network system known as the HPG axis. This axis is activated during the fetal and neonatal life, remaining in a quiescent state during childhood, and reactivating during puberty through adulthood.[3,9,10] Its principal regulator is gonadotrophin-releasing hormone (GnRH), a decapeptide hormone synthetized for the first time in 1971. GnRH is constituted by 10 amino acids and produced by a few parvocellular neurons,-10-30%, or less than 2000-, in the arcuate nucleus and hypothalamic preoptic area, extending all the way to the infundibular nucleus, to the lamina terminalis and, from that point, to the median eminence, which serves as a functional and anatomical link between the hypothalamus and the pituitary gland, thus allowing the GnRH to pass to the adenohypophysis through the hypophyseal portal system. This allows the GnRH to reach the pituitary gonadotropes and to stimulate its specific receptors or GnRHR.[1,3,5,9] GnRH controls and regulates the pituitary gonadotrophins hormones secretion, LH and follicle-stimulating hormone (FSH), which induce spermatogenesis and the production of testosterone (T), in the case of men, and stimulate gametogenesis in the ovaries and the production of the ovarian sex steroid hormones, estrogen ($E_2$) and progesterone (P), in the case of women.[1,3,9]

In women, the control of the reproductive cycle depends on an intricate interrelationship between GnRH, LH, FSH and ovarian steroids, which will also determine the release of GnRH, mainly from the arcuate nucleus, via feedback effects and loops that may be long, short or ultra-short. The first one takes place in, both, the hypothalamus, and the adenohypophysis, targeting the circulating levels of those hormones; the second one consists of a negative-feedback process that LH and FSH apply over their own secretion, most probably from an inhibitory effect from the hypothalamic releasing hormones; and, finally, the third one consists of an inhibition by the hypothalamic releasing hormones over their secretion. The regulation of the GnRH release also depends on the stimulatory or inhibitory actions of neurosignals or neurotransmitters such as dopamine, norepinephrine, epinephrine, endorphin, serotonin, melatonin, neuropeptide Y, kisspeptins, interleukin-1, gonadotropin-inhibitory hormone, as well as gonadal steroids, inhibin, activin, follistatin and environmental factors, such as stress and changes in energy stores.[1]

The secretion and release of GnRH follow two modes: pulsatile and surge, with the last one only taking place in females. The former refers to the secretion and episodic releases of the hormone, in a pulsatile manner, approximately every 30 to 120 minutes, into the hypophyseal portal system.[5,9–12] The adenohypophysis and GnRH neurons have an intrinsic pulsatile pattern. This pulsatile secretion depends on the hypothalamic expression of the GnRH-I gene.[1] Also, GnRH has the particularity that, apart from having a very short half-life, -2 to 4 minutes,[1,3,13] it is not quantifiable outside of the hypophyseal portal system. But LH and FSH do enter the peripheral circulation, so these hormones can be measured in venous blood.[14]

The pulsatility rate of release of GnRH is mainly controlled by a variety of hypothalamic neurons, especially those located on the arcuate nucleus; but, it may also be controlled by the neurons in the infundibular region, the preoptic area and/or the anteroventral periventricular nucleus,[3] and it has a physiological importance, since it avoids the downregulation of GnRHR in the pituitary gonaotropes; whereas, when GnRH is administered in a pulsatile way, there is an upregulation of the receptors. It is important to consider that LH and FSH are also secreted in a pulsatile manner, as well as the ovarian steroid hormones. FSH secretion is a product of low-frequency GnRH pulses, as opposed to LH secretion, which depends on high-frequency pulses. During the follicular phase of the menstrual cycle, the elevation of serum $E_2$ levels induces an activation of the HPG axis, which traduces itself in a higher GnRH pulse frequency secretion and, thus, augments the secretion levels of LH. However, when there are normal levels of $E_2$ and P, that pulsatility is negatively regulated, -with a downregulation of receptor numbers -, by those hormones, causing a maintenance of the basal levels of serum LH. Nevertheless, when the hormone levels have decreased, there is a lower GnRH pulse frequency secretion, causing an elevation of FSH levels. So, the effects induced by $E_2$ over GnRH pulsatility rate will be stimulatory or inhibitory, depending on the stage of the menstrual cycle, influencing the development of sex functions. More specifically, the LH pulse mean amplitude, on the early follicular phase, is of 6.5 IU/L, with a pulse mean frequency of 90 minutes; during the midfollicular phase, of 5 IU/L; during the late follicular phase, of 7.2 IU/L, with a pulse mean frequency of 60 to 70 minutes; during the early luteal phase, of 15 IU/L, with a pulse mean frequency of 100 minutes; during the midluteal phase, of 12.2 IU/L; and, on the late luteal phase, of 8 IU/L, with a pulse mean frequency of 200 minutes. On the other hand, P has an inhibitory action over the secretion of GnRH, especially over pulse frequency; nonetheless, it increases pulse amplitude during the luteal phase.[1,3,5,10,15]

### Gonadotropin-releasing hormone receptor (GnRHR)

The GnRHR is a rhodopsin-like G protein-coupled receptor[16] that has seven transmembrane domains, an extracellular amino-terminal domain with 35 amino acids and two glycosylation sites. This protein contains 328 amino acids and it is genetically encoded by 4q13, a gene located on the chromosome 4 that has three exons and two introns.[3,5,10] This receptor is not only found in the adenohypophysis–specifically in gonadotrophs, thyrotrophs and somatotrophs –, but also, on a multisystemic level, including the placenta, ovarian corpus luteum and granulose cells, epithelial ovarian carcinoma, endometrial, ovarian, and mammary cancer/carcinoma cell lines, prostatic tissue, and other organs, such as kidneys, liver, heart, skeletal muscle and mononuclear blood cells[10] There are a variety of GnRHRs, but GnRHR-1 is the only one expressed in mammals.[17]

There are certain differences between the GnRHRs located in the pituitary cells, -particularly in the gonadotrophs -, and those found in peripheral reproductive tissues. GnRHRs in the gonadotrophs are coupled to the Gαq/11 intracellular signaling pathway. Once GnRH binds to this receptor, phospholipase-Cβ1 is activated; thus, diacylglycerol (DAG) and inositol-1,4,5-triphosphate (IP3) are formed. This leads to the activation of protein kinase C (PKC) and increase of intracellular calcium levels, due to its release from endoplasmic reticulum, inducing the generation of action potentials that facilitate the biosynthesis, secretion, and release of gonadotropins. It is important to take into consideration that PKC also activates mitogen-activated protein kinase (MAPK) cascades, phospholipase D

and $A_2$, all of which are in charge of phosphorylating and activating a group of transcription factors that participate in the biosynthesis of gonadotropins. Also, it is known that GnRHR can be coupled to the Gαs/adenyl cyclase (AC) intracellular signaling pathway, which induces an increase of cyclic adenosine monophosphate (cAMP) levels and activates protein kinase A (PKA).[1,5,10,18–20]

In the peripheral reproductive tissues, particularly those in the female anatomy, the GnRHRs are coupled to Gαi intracellular signaling pathway. Once this pathway is triggered, a decrease of cAMP levels take place, activating protein kinase A (PKA). This will result in the activation of several other intracellular pathways, including, but not limited to, MAPK/ERK kinase, phosphoinositide 3-kinase (PI3K) and extracellular signal-regulated kinase 1/2 (ERK 1/2), which will inhibit cell proliferation, downregulate gene transcription and produce proapoptotic effects.[5]

In order for the GnRHR to be activated, there must be a hypothalamic pulsatile GnRH secretion,[3,18] whose frequency, width and shape will differ and vary, depending on the physiological conditions or menstrual cycle stage taking place at the moment.[21] Following the activation of this receptor, GnRHR internalizes slowly; plus, it does not undergo a fast desensitization.[5] However, when this receptor is not sufficiently stimulated – meaning that there is a decline on its stimulation-, the number of GnRHRs decreases, causing an induction and restoration of their initial number, via calcium mobilization, in case there is a subsequent stimulation to these receptors. This process is known as upregulation. But, when it is continuously stimulated, the number of GnRHRs will be downregulated, which will inhibit the synthesis and secretion of gonadotropins, a process known as desensitization.[10]

## Endometriosis and adenomyosis

Endometriosis is a chronic, estrogen-dependent, inflammatory disease, characterized by implantation, abnormal growth, and presence of endometrium-like tissue epithelium and stroma outside of the uterus,[2,22–24] mainly on the ovaries, uterine tubes, uterosacral ligaments, rectouterine or vesicouterine pouch, bladder, and/or intestines, and rarely on the diaphragm, umbilicus, lungs and pleura, pericardium, and brain.[2,3,23,24] The patient may present mild, severe, or intense symptoms, or even be asymptomatic, with dysmenorrhea, chronic non-menstrual pelvic pain, and dyspareunia being the most prevalent. Other infrequent symptoms are dysuria, dyschezia, constipation, and pain at ovulation. Endometriosis may also lead to subfertility and infertility, decreasing ovarian reserve and gamete transport.[2,22–26]

Adenomyosis, one of the leading causes of abnormal uterine bleeding, is another common gynecologic, chronic, inflammatory, estrogen-dependent, and benign uterine disorder in women of reproductive age,[27–29] particularly between the ages of 40 and 50, where heterotopic and non-neoplastic endometrial glands and stroma can be found in the myometrium, at a depth of more than 2.5mm, with surrounding fibrotic, hypertrophic and hyperplastic smooth muscle, causing the enlargement of the uterus.[27,29] It is characterized by the presence of heavy menstrual bleeding, dysmenorrhea, dyspareunia, pelvic pain, metrorrhagia, and infertility.[27,28]

Oral GnRH antagonists have proven to be a potential alternative for the treatment of these estrogen-dependent conditions, allowing a dose-dependent control of estradiol ($E_2$) levels,[22] including elagolix, an oral, nonpeptide GnRH antagonist, with a half-life of 4 to 6 hours,[4,8] and a rapid onset of action. Since its approval by the FDA in July 2018, elagolix has become the first GnRH antagonist used for the management and treatment of moderate to severe endometriosis-associated pelvic pain and dysmenorrhea, as well as dyspareunia, due to its high binding affinity for GnRHR, decreased interactions with hepatic P450 enzymes, avoidance of the flare-up effect of the GnRH agonists, and its efficacy in suppressing LH, FSH and $E_2$ levels.[2,22–25,28,30–32]

Elagolix is given at doses of 150mg once a day during a 24 month-period, causing partial estrogen suppression, and 200 mg twice a day for 6 months, resulting in full estrogen suppression, allowing an adequate and individual control of hypoestrogenic side effects.[4,22,32] The tablet should be taken at approximately the same time, every day, with or without food. Neither the regularity of the menstrual cycles nor the patient's body mass determines the efficacy of this GnRH antagonist.[32] It may potentially cause dose-dependent changes in menstrual patterns; increase risks of spontaneous abortions; decrease bone mineral density; increase transaminase levels; hot flushes; mood swings, among other mild side effects.[22,24,31] However, the use of this GnRH antagonist has proven to be significantly safe and well-tolerated, with prominent and sustained results that may arise after 4 weeks of treatment (Table 1).[2,3,31,33–36]

**Table 1** Summary of clinical trials and studies regarding the use of GnRH antagonists in different gynecological conditions

| Authors, year, country | Study design | Subjects | Intervention | Results |
|---|---|---|---|---|
| Diamond et al.,[33] | Phase II, randomized, double-blind, placebo-controlled, parallel group study. | n = 155 women with laparoscopically confirmed endometriosis within 8 years of screening (ages 18-49 years); Composite Pelvic Signs and Symptoms Score ≥ 6, moderate dysmenorrhea ≥ 2, mild non-menstrual pelvic pain ≥ 1. | -Subjects randomized to placebo, elagolix 150 mg or elagolix 250 mg once daily for 12 weeks. | - Elagolix: acceptable efficacy and safety profile. |
| | | | - Placebo group: rerandomized to elagolix. | - Monthly mean (standard error of the mean) reductions: not statistically different between placebo (-0.88 ± 0.18), elagolix 150 mg (-1.19 ± 0.18) and elagolix 250 mg (-1.25 ± 0.18); although, slightly greater in both elagolix groups. |
| | | | - Elagolix (150 and 250 mg) group: continue dosing for 12 more weeks. | - Monthly mean dysmenorrhea and non-menstrual pelvic pain scores reductions: greater in elagolix group, at 8 and 12 weeks ($p < 0.05$). |

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Table Continued...

| Authors, year, country | Study design | Subjects | Intervention | Results |
|---|---|---|---|---|
| | | | - Posttreatment follow-up period after 24 weeks, for 6 more weeks. | - Adverse effects: headaches, nausea, anxiety and hot flushes (elagolix 150 mg: 62.7%; elagolix 250 mg: 51.9%); minimal bone mineral density changes. |
| Carr et al.,[34] | Phase II, randomized, double-blind, multicenter, placebo-controlled, parallel group study. | n = 155 women with laparoscopically confirmed endometriosis within 8 years of screening (ages 18-49 years); Composite Pelvic Signs and Symptoms Score > 6, moderate dysmenorrhea > 2, mild non-menstrual pelvic pain > 1. | - Data collection for 8 weeks, establishing baseline pelvic pain. | - Elagolix: generally well-tolerated. |
| | | | - Double-blind placebo-controlled treatment period for 8 more weeks. | - Monthly mean dysmenorrhea, non-menstrual pelvic pain, and dyspareunia reductions, at week 8: statistically greater in elagolix group, compared with placebo (-1.13 ± 0.11, $p < 0.05$; -0.47 ± 0.07, $p < 0.05$; -0.61 ± 0.1, $p < 0.05$, respectively), with similar results at the end of the open-labeled period, and statistically greater than those at the end of week 30. |
| | | | - Open-label treatment period for 16 weeks: elagolix 150 mg for all patients once daily. | - Statistical improvement of quality-of-life measures. |
| | | | - Posttreatment follow-up period for 6 more weeks. | - Adverse effects: headache, nausea, and hot flushes (9.9% of patients, each). |
| Taylor et al.,[35] | Two phase III, double-blind, randomized trials (ELARIS EM-I and ELARIS EM-II). | n = 872 women with laparoscopically confirmed endometriosis within 10 years of screening (ages 18-49 years), with moderate or severe endometriosis-associated pain. | - Subjects randomized to elagolix 150 mg once daily or elagolix 200 mg twice daily, compared with a placebo group. | - Elagolix: acceptable efficacy and safety profile. |
| | | | - Clinical response to dysmenorrhea and to non-menstrual pelvic pain: measured after 3 months and 6 months, respectively, studying the possible decrease in the pain score and in the use of rescue analgesic agents. | - ELARIS EM-I: clinical response to dysmenorrhea at 3 months: elagolix 150 mg group (46.4%) and elagolix 200 mg group (75.8%) vs. placebo group (19.6%); clinical response to non-menstrual pelvic pain at 3 months: elagolix 150 mg group (50.4%) and elagolix 200 mg group (54.5%) vs. placebo group (36.5%); sustained responses at 6 months. |
| | | | | - ELARIS EM-II: clinical response to dysmenorrhea at 3 months: elagolix 150 mg group (43.4%) and elagolix 200 mg group (72.4%) vs. placebo group (22.7%); clinical response to non-menstrual pelvic pain at 3 months: elagolix 150 mg group (49.8%) and elagolix 200 mg group (57.8%) vs. placebo group (36.5%); sustained responses at 6 months. |
| | | | | - Adverse effects: hot flushes, higher level of serum lipids, and loss of bone mineral density. |
| Surrey et al.,[36] | Two phase III, double-blind, randomized trials (ELARIS EM-III and ELARIS EM-IV). | n = 569 women from the ELARIS EM-I and ELARIS EM-II trials. | - Evaluation of 6 additional months from the ELARIS EM-I and ELARIS EM-II trials, for a grand total of 12 months. | - Elagolix: acceptable efficacy and consistent safety profile, with sustained reductions in dysmenorrhea, non-mnestrual pelvic pain and dyspareunia. |

Table Continued...

| Authors, year, country | Study design | Subjects | Intervention | Results |
|---|---|---|---|---|
| | | | - Clinical response to dysmenorrhea, non-menstrual pelvic pain, and dyspareunia, measured after 6 months studying the possible decrease in the pain score and in the use of rescue analgesic agents, after a total of 12 months. | - ELARIS EM-I: clinical response to dysmenorrhea at 3 months: elagolix 150 mg group (52.1%) and elagolix 200 mg group (78.1%); clinical response to non-menstrual pelvic pain at 3 months: elagolix 150 mg group (67.8%) and elagolix 200 mg group (69.1%); clinical response to dyspareunia: elagolix 150 mg group (45.2%) and elagolix 200 mg group (60.0%).<br><br>- ELARIS EM-II: clinical response to dysmenorrhea at 3 months: elagolix 150 mg group (50.8%) and elagolix 200 mg group (75.9%); clinical response to non-menstrual pelvic pain at 3 months: elagolix 150 mg group (66.4%) and elagolix 200 mg group (67.2%); clinical response to dyspareunia: elagolix 150 mg group (45.9%) and elagolix 200 mg group (58.1%).<br><br>- Reduced estrogen levels. |
| Muneyyirci-Delale et al.,[37] | Two phase III, double-blind, randomized, placebo-controlled trials (ELARIS UF-I and ELARIS UF-II). | n = 790 premenopausal women (18-51 years) with heavy menstrual bleeding (> 80 ml menstrual blood loss per cycle), uterine fibroids and coexisting adenomyosis, diagnosed by magnetic resonance imaging and/or ultrasound at baseline. | - Subjects randomized to placebo, elagolix 300 mg twice daily or elagolix 300 mg twice daily + 1 mg estradiol / 0.5 mg norethindrone acetate once daily.<br><br>- Clinical response to heavy menstrual bleeding: measured after 6 months, studying the possible decrease in the pain score. | - Elagolix 300 mg BID + 1 mg estradiol / 0.5 mg norethindrone acetate: prominent results for the reduction of heavy menstrual bleeding; further studies required.<br><br>- Clinical response to heavy menstrual bleeding at 6 months: elagolix 300 mg BID + 1 mg estradiol / 0.5 mg norethindrone acetate group (76.8%) vs placebo group (12.1%) ($p < 0.05$).<br><br>- Adverse effects: hot flushes, headache, nausea, and night sweats. |
| Muneyyirci-Delale et al.,[38] | Two phase III, double-blind, randomized, placebo-controlled trials (ELARIS UF-I and ELARIS UF-II). | n = 786 premenopausal women (18-51 years) with heavy menstrual bleeding (> 80 ml menstrual blood loss per cycle), uterine fibroids, with and without coexisting adenomyosis, diagnosed by magnetic resonance imaging and/or ultrasound at baseline. | - Subjects randomized to placebo, elagolix 300 mg twice daily or elagolix 300 mg twice daily + 1 mg estradiol / 0.5 mg norethindrone acetate once daily.<br><br>- Clinical response to heavy menstrual bleeding: measured after 6 months, studying the possible decrease in the pain score. | - Elagolix 300 mg BID + 1 mg estradiol / 0.5 mg norethindrone acetate: prominent results for the reduction of heavy menstrual bleeding in patients with uterine fibroids and coexisting adenomyosis.<br><br>- Clinical response to heavy menstrual bleeding at 6 months in patients with adenomyosis (n = 126; 16%): elagolix 300 mg BID + 1 mg estradiol / 0.5 mg norethindrone acetate group (77.1%) vs placebo group (12.2%).<br><br>- Adverse effects: hot flushes, nausea, and night sweats. |

Table Continued...

| Authors, year, country | Study design | Subjects | Intervention | Results |
|---|---|---|---|---|
| Osuga et al.,[40] | Phase II, multicenter, randomized, double-blind, placebo-controlled study. | n = 487 premenopausal women, with regular menstrual cycles (25-38 days), with confirmed endometriosis via laparoscopy, laparotomy or magnetic resonance imaging, within 5 years of screening (ages 20-50 years); dysmenorrhea and/or pelvic pain. | - Subjects randomized to placebo, relugolix 10 mg once daily, relugolix 20 mg once daily, relugolix 40 mg once daily, or leuprorelin 3.75 mg as a monthly subcutaneous injection. | - Relugolix, orally administered: well-tolerated, prominent effects in the reduction of pelvic pain. |
| | | | - Clinical response to pelvic pain, dysmenorrhea, and dyspareunia, in mean visual analog scale score, during 28 days before the end of the 12-weeks treatment. | - Mean changes from baseline in mean visual analog scale score for pelvic pain: placebo group: -3.8 mm; relugolix 10 mg group: -6.2 mm; relugolix 20 mg group: -8.1 mm; relugolix 40 mg group: -10.4 mm; and leuprorelin group: -10.6 mm ($p < 0.05$). After the first month of treatment: said score started diminishing in a dose-response fashion, as well as in the case of dysmenorrhea. Regarding dyspareunia, results were not consistent. |
| | | | | - Estradiol, LH, FSH and progesterone: decrease in a dose-response fashion in relugolix groups. |
| | | | | - Adverse effects: hot flushes, metrorrhagia, menorrhagia, and bone mineral density decrease. |
| Osuga et al.,[41] | A phase III, multicenter, randomized, double-blind, double-dummy, active-controlled study | n = 454 premenopausal women, with regular menstrual cycles (25-38 days), with at least one of the following diagnostics: confirmed endometriosis via laparoscopy or laparotomy within 5 years of screening; clinical endometriosis with restricted uterine mobility; ovarian endometrioma confirmed via ultrasonography or magnetic resonance imaging, within 1 year of screening; pelvic pain; and/or induration of the Douglas cavity (ages 20-50 years); dysmenorrhea and/or pelvic pain. | - Subjects randomized to placebo, relugolix 40 mg once daily, or leuprorelin 3.75 or 1.88 mg as a monthly subcutaneous injection. | - Efficacy for treating pelvic pain: relugolix has a similar efficacy than leuprorelin, confirming the results of the phase II trial. |
| | | | - Clinical response to pelvic pain, dysmenorrhea, and dyspareunia, in mean visual analog scale score, during 28 days before the end of the 24-weeks treatment. | - Mean changes from baseline in mean visual analog scale score for pelvic pain: relugolix 40 mg group: -52.6 ± 1.3; and leuprorelin group: -57.5 ± 1.4; with a decrease of ovarian endometrioma of: 12.26 ± 17.52 cm3 (relugolix group) and 14.10 ± 18.81 cm3 (leuprorelin groups). Dysmenorrhea and dyspareunia had consistently similar results. |
| | | | | - Adverse effects: hot flushes, metrorrhagia, headache, and genital hemorrhage. |
| Donnez et al.,[22] | Phase IIb, multinational, multicenter, double-blind, randomized, parallel-group, placebo-controlled, dose-ranging trial (EDELWEISS trial). | n = 328 premenopausal women, with surgically confirmed endometriosis within 10 years of screening, and endometriosis-associated pain (ages 18-45 years). | - Subjects randomized to placebo, linzagolix 50 mg, linzagolix 75 mg, linzagolix 100 mg or linzagolix 200 mg, or a titrated-dose group (75 mg initially) once daily for 24 weeks. | - Linzagolix: well-tolerated, acceptable efficacy and safe profile, particularly in the reduction of endometriosis-associated pain and bone mineral loss and increase of quality of life. |

Table Continued...

| Authors, year, country | Study design | Subjects | Intervention | Results |
|---|---|---|---|---|
| | | | - Placebo group (12 weeks): rerandomized to linzagolix 100 mg group for another 12 weeks. | - Decrease in pelvic pain at 12 weeks: placebo group (34.5%); linzagolix 75 mg group (61.5%); linzagolix 100 mg group (56.4%); and linzagolix 200 mg group (56.3%), effects that were maintained up to 24 weeks. |
| | | | - Tritrated-dose group: 75 mg once daily for 12 weeks; 50, 75 or 100 mg for the next 12 weeks. | - Decrease in dysmenorrhea and non-menstrual pelvic pain: IDEM. |
| | | | - Clinical response to pelvic pain, non-menstrual pelvic pain, dysmenorrhea, amenorrhea, quality of life and bone mineral density. | - Statistical improvement of quality-of-life measures. |
| | | | | - Bone mineral density loss: less than 1% in linzagolix 50 and 75 mg groups, increasing dose-dependently up to 2.6% in linzagolix 200 mg group. |
| Osuga et al.,[52] | Phase III, multicenter, randomized, double-blind, double-dummy, parallel-group, noninferiority study. | n = 429 premenopausal women, regular menstrual cycles (25-38 days), with confirmed noncalcified uterine leiomyomas with no prior surgical treatment, and heavy menstrual bleeding (at least 120 points on the pictorial blood loss assessment chart) for minimum three consecutive days. | -Subjects randomized to placebo, oral relugolix 40 mg once daily, or leuprorelin acetate 3.75 or 1.88 mg as a monthly subcutaneous injection, for 24 weeks. | - Relugolix in the improvement of heavy menstrual bleeding: well-tolerated and noninferior to monthly injected leuprorelin. |
| | | | - Posttreatment follow-up period after 24 weeks, for 4 more weeks. | - Mean pictorial blood loss assessment chart score at baseline: relugolix group (254.3) and leuprorelin group (263.7). |
| | | | - Clinical response to menstrual blood loss, myoma and uterine volumes, and hemoglobin levels. | - Weeks 6-12: % patients with said chart score of less than 10 was of 82.2% in the relugolix group, and 83.1% in the leuprorelin group (noninferiority margin: 15%; $p < 0.05$). Relugolix: earlier effect on menstrual bleeding (chart score of less than 10: 64.2% vs 31.7%); faster recovery after treatment discontinuation (37 days vs 65 days). |
| | | | | - Myoma and uterine volumes reduced, hemoglobin levels increased. |
| Hoshiai et al.,[51] | Phase II, randomized, double-blind, placebo-controlled study. | n = 216 women, with confirmed uterine leiomyomas and heavy menstrual bleeding (at least 120 points on the pictorial blood loss assessment chart). | -Subjects randomized to oral relugolix 10 mg, 20 mg, or 40 mg once daily, for 12 weeks. | - Relugolix: well-tolerated and significant dose-dependent decreases in heavy menstrual bleeding. |
| | | | - Clinical response to menstrual blood loss, amenorrhea, myoma and uterine volumes. | - Points on the pictorial blood loss assessment chart score of less than 10 (weeks 6-12): relugolix 10 mg group (20.8%), 20 mg group (43.6%), and 40 mg group (83.6%). |
| | | | | - Relugolix 40 mg group: achievement of amenorrhea and dose-dependent decrease in myoma and uterine volumes. |
| | | | | - Adverse effects: mild-to-moderate headaches, menorrhagia, metrorrhagia and hot flushes. |

Table Continued...

| Authors, year, country | Study design | Subjects | Intervention | Results |
|---|---|---|---|---|
| Archer et al.,[53] | Phase IIa, multiple-cohort, proof-of-concept, dose-ranging study. | n = 271 women (mean age: 41.8 years), with regular menstrual cycles (24-35 days), with confirmed uterine leiomyomas via pelvic ultrasound, and heavy menstrual bleeding (> 80 ml menstrual blood loss per cycle). | - Subjects randomized to placebo (elagolix 600 mg once daily), elagolix 100 mg twice daily, elagolix 200 mg twice daily, elagolix 300 mg twice daily, elagolix 400 mg once daily, or elagolix 200 mg twice daily + continuous low-dose 0.5 mg estradiol / 0.1 mg norethindrone acetate, elagolix 300 mg twice daily + 1 mg estradiol continuously and 200 mg cyclical progesterone, for 3 months. | - Elagolix: well-tolerated and significant reduction in heavy menstrual bleeding in women with uterine fibroids; low-dose add-back regimes: decrease in flushing. |
| | | | - Clinical response to heavy menstrual bleeding: least-mean percentage changes of menstrual blood loss measured at the end of treatment. | - Mean percentage changes of menstrual blood loss: higher with elagolix (72-98%; greater with 300 mg), compared with placebo (8-41%); add-back regimes (80-85%). |
| | | | | - Adverse effects: hot flushes; lower with placebo (56%) and add-back regimes (55.6-70.6%). |
| Carr et al.,[54] | Phase IIb, double-blind, randomized, placebo-controlled, parallel-group study | n = 571 premenopausal, nonpregnant women (43±5 years), with regular menstrual cycles (less than 38 days), with confirmed uterine leiomyomas and heavy menstrual bleeding (> 80 ml menstrual blood loss per month). | - Subjects randomized to elagolix 300 mg once daily or 600 mg once daily, for 6 months. | - Elagolix (with add-back regime + without add-back regime): well-tolerated and significant reduction in heavy menstrual bleeding in women with uterine fibroids; add-back regime: reduction in hypoestrogenic effects in bone mineral density. |
| | | | - Elagolix 300 mg group: placebo, elagolix alone, elagolix + 0.5 mg estradiol / 0.1 mg norethindrone acetate, and elagolix + 1 mg estradiol / 0.5 mg norethindrone acetate. | - Heavy menstrual bleeding reduction: elagolix 300 mg group (placebo: 27%; elagolix alone: 92%; elagolix + 0.5 mg estradiol / 0.1 mg norethindrone acetate: 85%; and elagolix + 1 mg estradiol / 0.5 mg norethindrone acetate: 79%); elagolix 600 mg group (placebo: 32%; elagolix alone: 90%; elagolix + 0.5 mg estradiol / 0.1 mg norethindrone acetate: 73%; and elagolix + 1 mg estradiol / 0.5 mg norethindrone acetate: 82%). |
| | | | - Elagolix 600 mg group: placebo, elagolix alone, elagolix + 0.5 mg estradiol / 0.1 mg norethindrone acetate, and elagolix + 1 mg estradiol / 0.5 mg norethindrone acetate. | - Bone mineral density: reduction attenuated by the addition of elagolix + 1 mg estradiol / 0.5 mg norethindrone acetate. |
| | | | - Clinical response to heavy menstrual bleeding, and changes in bone mineral density. | |

Table Continued...

| Authors, year, country | Study design | Subjects | Intervention | Results |
|---|---|---|---|---|
| Schlaff et al.,[56] | Two phase III, double-blind, randomized, placebo-controlled trials (ELARIS UF-1 and ELARIS UF-2). | n = 412 premenopausal women (18-51 years), with regular menstrual cycles (24-35 days), with confirmed uterine leiomyomas via ultrasonopgraphy, and heavy menstrual bleeding (> 80 ml menstrual blood loss per cycle). | - Subjects randomized to placebo, elagolix alone 300 mg twice daily, or elagolix 300 mg twice daily + 1 mg estradiol / 0.5 mg norethindrone acetate once daily, for 6 months. | - Elagolix with add-back regime: well-tolerated and significant reduction in heavy menstrual bleeding in women with uterine fibroids. |
| | | | - Posttreatment follow-up period, for 12 more weeks. | - Heavy menstrual bleeding reduction in ELARIS UF-1: placebo (8.7%), elagolix alone (84.1%), and elagolix + estradiol / norethindrone acetate (68.5%). |
| | | | - Clinical response to heavy menstrual bleeding. | - Heavy menstrual bleeding reduction in ELARIS UF-1: placebo (10%), elagolix alone (77%), and elagolix + estradiol / norethindrone acetate (76.5%).<br>- Adverse effects: hot flushes and metrorrhagia, especially with the use of elagolix + 1 mg estradiol / 0.5 mg norethindrone acetate.<br>- Bone mineral density: reduction attenuated by the addition of elagolix + 1 mg estradiol / 0.5 mg norethindrone acetate. |

GnRH antagonists do not form part of the first line of treatment of adenomyosis. However, elagolix has been used in patients with uterine fibroids and adenomyosis at the baseline, with some consistent results, particularly a significant reduction of the heavy menstrual blood loss (Table 1).[37,38] In the first half of 2020, the first case report of a patient with adenomyosis, treated with elagolix, was published. Three months after the start of the treatment, at a dose of 150 mg once daily, the pelvic pain had ceased. One month later, the uterine mass had disappeared, with some diffusely distributed remnants. This case clearly shows the potential that elagolix may have in forming part of the line of treatment of adenomyosis.[39]

Relugolix and linzagolix are other oral GnRH antagonists that are currently in the third phase of clinical trials for the treatment of endometriosis-associated pelvic pain.[2] Relugolix (TAK-385) is a novel non-peptide, with a high affinity and a potent orally selective antagonist activity for human GnRHR. It can continuously and reversibly suppress the HPG axis.[3] The clinical trials have shown prominent results in the reduction of pelvic pain, after the oral administration of relugolix at doses of 10, 20, and 40mg, once a day, for 24 weeks, with some mild side effects, including metrorrhagia, menorrhagia, and hot flushes, as well as a decrease in $E_2$ levels after the administration of relugolix at higher doses. The third phase of ongoing clinical trials (SPIRIT 1, SPIRIT 2, and SPIRIT extension) is studying the efficacy and safety of the daily co-administration of 40 mg of this antagonist with 12 or 24 weeks of 1mg of estradiol and 0.5mg of norethindrone acetate as add-back therapy, in patients with endometriosis-associated pelvic pain (Table 1).[3,40–43]

Linzagolix, an antagonist with a half-life of 15 to 18 hours, has had potentially positive results in the alleviation of dysmenorrhea and endometriosis-associated pelvic pain, after its daily administration, at doses of 75, 100, and 200mg. Patients who presented with dyspareunia received higher doses (200mg), due to hypoestrogenic side effects. However, with that same high dose, bone mineral density loss would be a more frequent side effect, in comparison with lower doses (100 mg). The most common adverse effects have been headaches and hot flushes; increases in LDL cholesterol, HDL cholesterol, and triglyceride levels have not been commonly reported. It should be taken into account that, even though a phase II trial demonstrated the safety, efficacy and tolerance of linzagolix in the treatment of endometriosis, there are no definitive nor published results yet, considering that the EDELWEISS 3 phase III trial is still ongoing, and that the EDELWEISS 2 trial was discontinued due to the COVID-19 pandemic. Recently, it was shown that linzagolix may play a crucial role in the treatment of adenomyosis, causing a regression in the adenomyotic lesions, and improving the patient's quality of life. Nevertheless, at the moment, linzagolix, as well as GnRH antagonists in general, are not included as tools in the treatment of adenomyosis (Table 1).[2,27,44,45]

Another GnRH antagonist that is used for the treatment of endometriosis is cetrorelix acetate, a basic peptide that is subcutaneously injected.[3,42] It has the capacity of inhibiting the proliferation of tumor necrosis factor-α (TNF-α)-induced cells, and thus reducing its levels, in endometrial stromal cells,[3,31] as well as reducing the stromal and glandular components of endometriotic lesions.[17] In a recent clinical trial, 3mg of cetrorelix acetate were subcutaneously injected, each week, for two months, to a group of 15 patients with histologically diagnosed symptomatic endometriosis, showing positive results to this antagonist, with almost no adverse effects. 60% of the sample showed regression of endometriosis-associated lesions, making cetrorelix acetate a potential alternative for the treatment of this condition.[3,31,42]

## Uterine fibroids

Uterine fibroids, or leiomyomas, constitute the most common solid and benign gynecological tumors in women of reproductive

age, which arise from the myometrium, with the particularity of being steroid-hormone responsive and an unknown etiology, whose monoclonal growth depends on the presence of $E_2$ and P, secreting an excessive, altered, and disorganized extracellular matrix of fibrous nature. Leiomyomas can be classified as subserosal, intramural and submucosal. These patients have a prevalence of abnormal and excessive menstrual bleeding, intermenstrual bleeding, with or without dysmenorrhea, as well as a possible association with infertility and subfertility; although, some women are asymptomatic.[6,26,46]

Cetrorelix acetate, ganirelix acetate, and Nal-Glu have been studied for the treatment of leiomyomas, although these are not commonly used. Their administration is via a subcutaneous injection every 1 to 4 days.[46,47] The former has the potential of decreasing the uterine and the fibroids' volume in pre-menopausal patients, causing menorrhagia, the disappearance of pelvic pain, and a rapid return of ovarian function once the treatment has ceased. It is believed that it increases apoptotic processes, inhibits the proliferating cell nuclear antigen, and decreases the production of some of the extracellular components of leiomyomas, including collagen-1A, fibronectin and versican variant V0.[7,48]

In January 2019, the use of relugolix for the treatment of uterine fibroids was approved in Japan.[43] This orally active non-peptide GnRH antagonist is capable of inhibiting the secretion of LH and FSH and, thus, $E_2$ and P, inducing amenorrhea.[43,49] With an oral dosage of 40mg and a half-life of 45.42 hours, this antagonist allows faster recovery of the hormonal serum levels, inducing menstruation, after it is discontinued. The recovery of fertility in these patients tends to be faster than in those that are treated with GnRH agonists, such as leuprorelin acetate.[43,49,50] In a 2017 randomized, double-blind, phase II control trial, Hoshiai et al.[51] concluded that amenorrhea and a dose-dependent reduction of the volume of the uterus and the uterine fibroids tend to be achieved by the majority of patients treated with a dose of 40mg of relugolix, in comparison with those treated with 10 and 20mg, respectively, without presenting serious adverse effects. Osuga et al.[52] concluded, as well, in the results of two separate phase III, randomized clinical trials, published in March 2019[52] and November 2019,[49] respectively, that the use of 40mg of relugolix once a day to treat heavy menstrual bleeding and pain symptoms associated with uterine fibroids is absolutely safe and well tolerated, with non-severe side effects. In both trials, more than 50% of their sample achieved either the lowest possible score of pain or its complete abolition, and more than 80% presented a reduction of the volume of the uterus and the uterine fibroids. Amenorrhea was achieved by more than 75% of the sample at the end of the trials, and menstruation returned to patients once the treatment was discontinued. Patients also presented hypoestrogenic effects and reduction of the levels of LH, FSH, and P, which returned to normality after the discontinuation of relugolix, a clear advantage that GnRH antagonists have over agonists, especially for the restoration of fertility. At the moment, three international phase three clinical trials are studying the efficacy and safety of the use of 40mg relugolix co-administered, once a day, with add-back therapy with low doses of estradiol and norethindrone acetate. These trials are LIBERTY 1, LIBERTY 2, and LIBERTY extension (Table 1).[43,49]

In 2017, Archer et al.[53] published the results of a phase II study, demonstrating that the use of 200-600mg of elagolix alone in premenopausal women with uterine fibroids and heavy menstrual blood loss is similar than the use of elagolix with a low-dose hormonal ($E_2$ and P) add-back therapy for the suppression of heavy menstrual bleeding and reductions of the sizes of the uterine cavity and fibroids. On the other hand, Carr et al.,[54] in 2018, demonstrated that the use of elagolix alone, - 300mg twice daily and 600mg once a day, - is superior for reducing profuse menstrual blood loss in women with leiomyomas, compared with elagolix with hormonal add-back therapy (0.5mg of estradiol/0.1mg of norethindrone acetate and 1mg of estradiol/0.5mg of norethindrone acetate). Hypoestrogenic side effects, especially on bone mineral density, were reduced with the use of hormonal add-back therapy.[54] The ELARIS Uterine Fibroids (UF) 1 and 2 randomized, double-blind, placebo-control, phase III clinical trials demonstrated that the reduction of mean menstrual blood loss volume after one month of treatment, achievement of amenorrhea, and improvement of quality of life is completely significant in women treated with elagolix and add-back therapy, with mild to moderate side effects.[55–57] In the first half of 2020, the FDA approved the first and only oral treatment for heavy menstrual bleeding associated with uterine fibroids, marketed as Oriahnn, which consists of two capsules; the first one contains 300mg of elagolix, 1 mg of estradiol and 0.5 mg of norethindrone acetate, which is taken in the morning; and the other one contains elagolix alone, which is taken at night. This treatment should be received for a maximum of 24 months, reducing heavy menstrual bleeding, and decreasing hypoestrogenic side effects (Table 1).[58,59]

Finally, even though more studies are required in the future, linzagolix with add-back therapy may constitute the most appropriate regime for the treatment of sex-hormone-dependent diseases, including uterine fibroids with heavy menstrual bleeding, considering that it has shown rapid, dose-dependent decreases in the serum levels of LH, FSH, and $E_2$. This was demonstrated by Pohl et al.,[26] in 2019, with a randomized, phase I clinical trial, that showed that the use of coadjuvant add-back therapy may be necessary with the use of higher doses of linzagolix, in order to avoid an increase in the patients' bleeding patterns, $E_2$ levels, and adverse effects. Although, the small sample of the study (n=32) may be a limitation and must be taken into account. Overall, linzagolix has been well tolerated, with mild to moderate severe effects, especially hot flushes and bone mineral loss.[26]

## Precocious puberty

The development of secondary sexual characteristics before the expected age is what defines precocious puberty (PP), usually taking place before the age of 8 in girls, and 9 in boys. PP can be GnRH-independent or peripheral (PPP), or GnRH-dependent or central (CPP).[60,61] PPP is a congenital or acquired consequence of sex steroid hormones secretion from the gonads, adrenal cortex, or ectopic sources, characterized by an abnormally increased production of estrogens, and androgens. It is less common than CPP and it can sometimes lead to the pulsatile secretion of GnRH and secondary central PP.[61,62] CPP can be caused by genetic mutations, injuries, malformations, idiopathic, and different pathologies of the central nervous system. Its incidence is similar in girls and boys.[1,63] In girls, the main indicator is breast development or an increase in the growing speed; this can be accompanied by pubic hair development and an increase in uterine volume. In boys, it usually presents as an increase in testicular volume; although, gonadarche can precede adrenarche in boys under the age of 6.[1,64,65]

Even though the treatment of CPP is usually based on GnRH agonists, recent studies have shown that the use of GnRH antagonists, such as relugolix, may be an effective treatment for this disorder. GnRH antagonists offer some advantages over agonists.[66] As it was previously mentioned, GnRH agonists may cause clinical symptoms related to an initial increase of gonadotropins and gonadal hormones;

the antagonists, on the other hand, reduce these hormones, avoiding the flare-up caused by the agonists, and therefore diminishing this side effect.[67] One of these drugs is relugolix, a selective antagonist that is capable of reducing the levels of $E_2$, P, and T in a short period.[43] Another advantage of relugolix is that, as a non-peptide antagonist, after its withdrawal and discontinuation, the patient rapidly regains gonadal function, avoiding undesirable adverse effects. There are no definitive results regarding the use of relugolix in PP, as a first-line treatment. This may serve as a prominent study in these patients in a non-distant future.[1]

### Infertility

Since the '90s, GnRH antagonists have been used to suppress hypophyseal activity and the HPG axis, preventing premature LH surges,[68] when used as comedication in IVF/intracytoplasmatic sperm injections procedures (IVF/ICSI).[69] In comparison with GnRH agonists, the duration of treatment with GnRH antagonists is shorter. There is a reduction of gonadotropin dose requirements and duration of its stimulation. There is less suppression in the early stages of the follicular phase, benefiting women who are poor responders to these treatment protocols. Considering that the levels of LH decrease during the mid-follicular phase and finally start gradually ascending again in the late follicular phase of the menstrual cycle, these protocols should be applied during these phases of the menstrual cycle, due to its major risk of a premature rise in the LH levels. However, the suppression of endogenous gonadotropin secretion is more complete with the use of antagonists than with the use of agonists. This treatment can also be postponed until the follicular development and the elevation of the $E_2$ levels have taken place, avoiding the emergence of hypoestrogenic side effects, approximately after 5 to 6 days posterior to gonadotropin stimulation. The use of GnRH antagonists diminishes the risk of ovarian hyperstimulation syndrome, development of follicular cysts, and cycle cancelation. However, patients have a risk of treatment failure of around 0.34 and 8%, considering that the release of GnRH induced by endogenous $E_2$ is still preserved. Among the most prominent risk factors for these patients are senescence, diminished ovarian reserve, and a decreased response to gonadotropin.[1,4,68]

Since 1995, cetrorelix and ganirelix have been used as comedication in ovarian stimulation for IVF. There are two forms of administration of these GnRH antagonists. The first one is the single-dose protocol, which consists of the injection of 3mg of cetrorelix once daily, during the late phase of ovarian stimulation. And the second form is the multiple-dose protocol, consisting of the administration of 0.25µg of either cetrorelix or ganirelix starting on the sixth day of stimulation. Nonetheless, since the introduction of a flexible regimen starting on day 7, which is based on the size of the follicle, the number of injections and the duration of the treatment with these drugs have diminished. Even though clinical trials in the past evidenced a small reduction in pregnancy rates, when GnRH antagonists were applied, protocols used in the present day have not shown any difference in the rates of live births.[4,69] Usually, there is no variation in terms of adverse effects differences between women using GnRH antagonists and those using agonists.[4] Embryonic side effects, as well as a decrease in their development and implantation potential, may arise if there is no increase in the P secretion levels after the immediate suppression of the LH by the GnRH antagonist.[69]

Lambalk et al.[8] showed that GnRH antagonists regimes, compared with agonists, especially in patients with polycystic ovarian syndrome, reduced by 2.5% the rate of ovarian hyperstimulation syndrome, with a 3.6% of risk reduction in ongoing pregnancy rates, possibly due to inadequate suppression of the LH surges or to the lowering of the oocyte yield, as a result of asynchronous follicular development in response to endogenous FSH secretion during the early follicular phase. But this sample was treated with GnRH antagonists and received an oral contraceptive pill pretreatment,[7] which might have altered their results, considering that this pretreatment is capable of reducing the chances of ongoing pregnancy and causing lower live-birth rate, demonstrated by Kolanska et al.[70,71] In recent years, steroid pretreatments in IVF procedures, such as the luteal estradiol pretreatment, during the GnRH antagonist protocol, have been showing prominent results, by improving follicle stimulation, retrieving oocyte maturation, improving the response to the GnRH antagonists in the IVF cycles, and, even, clinical pregnancy and live birth rates. Future clinical trials are needed to get better conclusions.[72]

## Conclusion

GnRH antagonists have proven to be promising alternatives in the treatment of estrogen-dependent conditions, such as endometriosis, adenomyosis, and uterine fibroids, through the control of the non-menstrual pelvic pain and heavy menstrual bleeding that arise from these pathologies. Considering that these drugs have advantages over GnRH agonists, particularly the avoidance of the flare-up effects that are experienced with the use of the agonists, as well as their immediate therapeutic effects and the suppression of the premature surges of LH levels, GnRH antagonists have shown great potential in the treatment of endocrine pathologies, including PP. They have also been used in IVF/ICSI procedures, diminishing the risks of ovarian hyperstimulation syndrome, with a small or no reduction in pregnancy rates. These drugs have proven to be promising alternatives in the treatment of these pathologies and may eventually be used as their first line of treatment, as long as they are administered following their administration protocols correctly. In that sense, it is imperative to keep enhancing and applying new clinical trials regarding the use of GnRH antagonists.

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The authors declare that there is no conflict of interest regarding the publication of this article.

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