SPECIAL ISSUE

Clinical applications of gonadotropin-releasing hormone analogues: a broad impact on reproductive medicine

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Gonadotropin-releasing hormone (GnRH) is central to the control of the entire hypothalamic-pituitary-gonadal axis. Manipulation of GnRH, in turn, regulates pituitary response and ovarian hormone production. Gonadotropin-releasing hormone analogues have revolutionized assisted reproductive technology and gynecologic practice. The recent advent of oral GnRH antagonists with an inherent rapid onset of action continues to transform the treatment options available for several common gynecologic conditions, including endometriosis and fibroids. Herein, we review neuroendocrine GnRH activity and discuss modulation of the reproductive axis by GnRH analogues for diverse clinical applications. (Fertil Steril Rep® 2023;■:■–■. ©2023 by American Society for Reproductive Medicine.)

Key Words: Gonadotropin-releasing hormone, GnRH, GnRH analogue, infertility, endometriosis

THE ROLE OF GnRH IN PHYSIOLOGY

Gonadotropin-releasing hormone (GnRH)–containing neurons are located in the hypothalamus and are thought to be largely quiescent during childhood until the onset of reproductive years (1). In the peripubertal transition, peripheral and neuronal cues modulate the GnRH neurons of the hypothalamus. After the onset of puberty, GnRH production and release are highly regulated. Gonadotropin-releasing hormone has a short half-life of 2–4 minutes and is secreted in frequent pulse waves. Once secreted from the hypothalamus, GnRH, in turn, controls pituitary follicle-stimulating hormone (FSH) and luteinizing hormone (LH) release through stimulation of the gonadotropin-releasing hormone receptor (GnRH-R), a G-coupled protein receptor in the pituitary (2, 3). As ovarian hormones estrogen and progesterone are released in response to FSH/LH stimulation, the GnRH neurons in the hypothalamus sense circulating peripheral sex steroid hormone levels and respond via negative and positive feedback. A thorough understanding of GnRH release and effect on hormonal regulation has evolved over the last 50 years since the elucidation of GnRH neuronal activity in the 1970s (4). Building on this understanding, regulation of GnRH and the GnRH-R has rapidly advanced fertility and clinical gynecologic care.

REVIEW OF GnRH AGONISTS AND ANTAGONISTS

Given the short half-life of GnRH due to peptidases, a clinically useful analogue requires modification to evade degradation. Gonadotropin-releasing hormone agonists have amino acid modifications at the location where peptide cleavage typically occurs and, therefore, have longer half-lives (3). The mechanism of action of GnRH agonists is dependent on paradoxical modulation, resulting in a functional antagonism of the GnRH-R. Specifically, once the GnRH-R is stimulated by a GnRH agonist, there is an initial increase in FSH and LH release, known as the "flare effect." However, with sustained GnRH agonist exposure over 1–3 weeks after initial stimulation, the GnRH-R is desensitized and becomes down-regulated and uncoupled from downstream signaling (3). Ultimately, without GnRH-R signaling capacity, the GnRH effect of

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the pituitary is mitigated, resulting in hypogonadotropic hypogonadism.

Gonadotropin-releasing hormone agonists trigger the GnRH-R and lead to initial gonadotropin release, whereas GnRH antagonists competitively bind to the GnRH-R and rapidly render it inactive. Because GnRH antagonists do not stimulate GnRH release, they are not associated with a flare and do not depend on receptor desensitization and down-regulation. As a result, there is a clinical response typically within 24 hours (3).

Interestingly, the first GnRH analogue developed in 1985 was leuprolide acetate, a GnRH agonist, which was initially approved for the treatment of prostate cancer. Therapeutic applications have progressed, and GnRH analogues currently have a diverse role in gynecologic care. Over the years, advances in the formulations and route of administration of GnRH have occurred. Current modes of delivery of GnRH agonists include injection, medication-releasing implants, and nasal spray. Gonadotropin-releasing hormone antagonists are administered by injection or in oral formulations (3, 5).

APPLICATION IN ASSISTED REPRODUCTIVE TECHNOLOGY

Anovulation due to a hypothalamic etiology is perhaps the most obvious application of GnRH agonists. Physiologic stimulation of 1 follicle can be mimicked through intravenous pulsatile GnRH administration. Specifically, the administration of parenteral GnRH simulates the pulse waves, which ultimately prompt gonadotropin release from the pituitary and leads to the development of a single ovarian follicle. Monofollicular development minimizes the risk of multiple gestation and ovarian hyperstimulation syndrome (OHSS) but is associated with practical challenges because it requires careful dosing via an indwelling intravenous catheter (3).

Moreover, GnRH analogues are used in the assisted reproductive technology (ART) protocols in an effort to retrieve multiple oocytes. In these protocols, LH and/or FSH analogues are first used to stimulate the ovaries for growth of multiple follicles. To prevent endogenous LH surge and subsequent ovulation before follicle retrieval, GnRH analogues are used to block pituitary-driven LH release (6). Such administration of GnRH analogues has been employed for the last 25 years in the clinical practice of ART. Both GnRH agonists and antagonists are used in these protocols, and selection of a particular analogue depends on the clinical scenario. Protocols with GnRH agonists are associated with increased pregnancy rates when compared with the use of gonadotropins alone for ovarian stimulation, largely due to the prevention of ovulation before oocyte retrieval (7).

Practices using GnRH agonists are grouped into "short" and "long" protocols. The GnRH "short" protocol capitalizes on the initial "flare" as an adjunct to exogenous LH/FSH administration. Alternatively, the "long" protocol is initiated in the midluteal phase of the preceding cycle, when pituitary stores of gonadotropins are lowest and progesterone provides pituitary feedback inhibition, and therefore, the impact of the "flare" effect is minimized. Gonadotropin-releasing hormone antagonists are more frequently used in contemporary ART. Antagonists are advantageous in ART because they also do not stimulate the "flare" effect. Generally considered a more patient-friendly protocol, the GnRH antagonist protocols are associated with a shorter cycle length and time of GnRH analogue therapy and lower risks of follicular cyst development and OHSS (3, 6). In practice, the GnRH antagonist is started either approximately 6 days after the start of stimulation or when the leading follicle size reaches 12–14 mm. More recently, GnRH agonists have been used to trigger oocyte maturation. After follicular development, a bolus of GnRH agonist can be used to stimulate the release of LH and follicular maturation. The rapid peak followed by a precipitous drop in the serum LH level that follows a GnRH trigger mimics a physiologic, endogenous LH surge at ovulation. Gonadotropin-releasing hormone agonist ovulation triggers are preferred over human chorionic gonadotropin in patients at risk for OHSS because the longer half-life of human chorionic gonadotropin can prompt continued stimulation of the LH receptor and increase the risk of OHSS.

USE OF GnRH ANALOGUES IN ENDOMETRIOSIS

Endometriosis is a chronic condition defined as the presence of endometrial tissue outside of the uterus. Approximately 5%–10% of all reproductive-age females have endometriosis. In patients seeking gynecologic care for pelvic pain or infertility, up to 50% are suspected to have underlying endometriosis (8, 9). The clinical sequelae associated with endometriosis are classically pelvic pain and infertility; however, recently, the systemic effects of endometriosis have become more widely appreciated. Endometriosis is now understood as a disease with multiple manifestations well beyond the reproductive tract and pelvis (8). Although surgical excision of endometriosis is both diagnostic and therapeutic and remains the preferred treatment for patients who are trying to conceive, guidelines have shifted to now recommend empiric medical therapy for suspected endometriosis in all other scenarios (10, 11). In addition to treating the pelvic pain associated with endometriosis, medical therapy may combat the systemic manifestations of the disease. Ectopic endometriosis tissue grows in response to hormonal stimulation, and therefore, targeted medical therapy is useful in suppressing endometriosis lesions by modulating the sex steroid hormone levels.

Gonadotropin-releasing hormone analogues are employed as a second-line medical therapy after failure to adequately respond to a combined oral contraceptives and nonsteroidal anti-inflammatory medications. These treatment regimens focus on decreasing hypothalamic-pituitary-ovarian (HPO) axis signaling and lowering the estradiol levels. If the estradiol levels are lowered but not completely eliminated, control of endometriosis may be achieved without inducing vasomotor symptoms or other sequelae of pseudomenopause, such as loss of bone mineral density. Alternatively, add-back therapy introduces small doses of hormonal therapy, similar to use for the treatment of menopausal symptoms, to maintain bone health and mitigate menopausal symptoms (3).

Gonadotropin-releasing hormone agonists and antagonists may be used with excellent efficacy in improvement of endometriosis symptoms (5, 12, 13). Both injectable GnRH agonists and oral GnRH antagonists are approved medical treatments for endometriosis. Higher-dose oral GnRH antagonist therapy has particular efficacy for improving dyspareunia symptoms and reduces analgesia use (5). Oral GnRH antagonists are advantageous for their rapid onset, absence of a flare effect, and convenience of oral dosing (3, 5). The introduction of oral antagonists truly highlighted the potential GnRH analogues and expanded their usage to a much wider array of patients, some of whom were reluctant to use an injectable medication. The ease of use, prompt onset of action, and rapid reversal of GnRH antagonists have led to widespread adoption in clinical practice.

Importantly, the advantages of GnRH antagonists have stimulated changes to treatment guidelines in the care of endometriosis by eliminating the need for a surgical diagnosis. Before the advent of oral GnRH antagonist therapy, medical therapy entailed a prolonged course of a depot GnRH agonist that could not be fully reversed for months, and practitioners and patients were reluctant to commit to such a therapy without a definitive surgical diagnosis. Now, the convenience of oral GnRH antagonists has made a trial of the routine practice of both first- and second-line medications. Gonadotropin-releasing hormone antagonist therapy has revolutionized endometriosis care and spares immediate surgical intervention for the greater than 30% or more of patients who fail first-line oral contraceptive therapy.

IMPROVING OUTCOMES FOR PATIENTS WITH FIBROIDS

Uterine fibroids, also known as leiomyomas, are common, benign, smooth muscle tumors of the uterus that arise via clonal expansion of abnormal myocytes (14). Women with fibroids often present with heavy menses, abnormal uterine bleeding, pelvic pressure, or impaired reproductive outcomes (14). Because fibroids are hormone-responsive, GnRH analogues have a role treatment and have been used in fibroid treatment since the 1980s (15). Currently, GnRH analogues continue to play a role in the management of fibroids (16). The GnRH agonist leuprolide has been shown to significantly reduce blood flow to the uterus and decrease uterine size (17), overall leading to a significant improvement in anemia associated with heavy uterine bleeding in the setting of fibroids (18). Similarly, several recently published studies have demonstrated that oral GnRH antagonists with add-back hormonal therapy significantly reduced heavy menstrual bleeding, regardless of the baseline uterus size or fibroid location (19–22). As aforementioned, these agents are oral and have the positive attributes of a rapid onset of action without a flare effect. Although oral contraceptives are commonly used as a first-line therapy for heavy menstrual bleeding associated with fibroids, they have no effect on fibroid growth and predominantly affect the endometrium. The convenience and superior efficacy of GnRH antagonists have made these drugs a first-line fibroid therapy.

If the decision is made for surgical management for a patient with large uterine fibroids, GnRH agonist therapy may be used for 3–4 months preoperatively to shrink fibroids, improve preoperative anemia, reduce intraoperative blood loss, and decrease the rates of surgical complications (23, 24). This is particularly useful in fertility-sparing surgery, such as abdominal myomectomy, which tends to have bleeding at the site of fibroid removal. In Europe, a GnRH antagonist is available without add-back therapy to achieve greater fibroid regression before surgery. Gonadotropin-releasing hormone antagonists at doses appropriate for fibroid treatment are not currently available in the United States without add-back therapy.

A ROLE FOR MOOD REGULATION IN PATIENTS WITH PREMENSTRUAL MOOD DISORDERS

Premenstrual syndrome (PMS) and premenstrual dysphoric disorder (PMDD) are conditions defined by mood dysregulation, which recurs cyclically in the luteal phase of the menstrual cycle (25). Premenstrual dysphoric disorder is a more advanced spectrum of PMS. The mainstay of treatment for PMS and PMDD are selective serotonin reuptake inhibitors, which typically have reasonable efficacy (26, 27).

Given the exacerbation of mood symptoms during the luteal phase, a progesterone mediated effect is thought to be driving mood changes. Therefore, hormonal modulation can also be employed. Oral contraceptive pills are used to prevent ovulation. Specifically, oral contraceptive pills containing the progestin drospirenone have been shown to improve PMDD symptoms. An early study of GnRH agonists in PMDD found that the administration of GnRH agonists improved symptoms significantly (28), and follow-up studies have suggested add-back therapy with daily estradiol and progestin every third month to minimize progestin-induced symptoms (25). To our knowledge, there have not been studies that have assessed the efficacy of GnRH antagonists on addressing PMS and PMDD; however, GnRH antagonists likely have a similar effect and may prove superior to progestin containing treatments or selective serotonin reuptake inhibitors.

GnRH AGONISTS HALT THE DEVELOPMENT OF PRECOCIOUS PUBERTY

Regulation of puberty requires a coordinated influence over GnRH secretion and pulsatility, which is thought to be mainly mediated by kisspeptin, a neuropeptide upstream of GnRH neurons in the hypothalamus. The sequence of pubertal progression in girls starts with thelarche, followed by adrenarche and then menarche (29). Precocious puberty can stunt height and increase the risk of medical and psychosocial comorbidities (30, 31). The diagnosis of precocious puberty is made through a combination of clinical assessment, hormonal evaluation, and imaging studies (32). Precocious puberty can be organized into 2 broad categories on the basis of the driving forces of early development: central and peripheral (29, 33). Interpretation of the gonadotropin and hormonal levels, as well as a GnRH stimulation test, can aid in distinguishing central vs. peripheral precocious puberty (32).

In central precocious puberty, the gonadotropin levels are elevated, stimulating the pubertal cascade. Therefore, GnRH analogues that function to decrease gonadotropin release by the pituitary are the main therapeutic strategy in central precocious puberty. There are several formulations of GnRH agonists that are used, and the treatment of central precocious puberty with GnRH agonists has been the gold-standard treatment for the last 40 years (32, 33). Histrelin subdermal implants offer 1 year of agonist therapy (34) and has the advantage of evading monthly injections. The formulation of GnRH agonist therapy chosen is per physician and patient preference (35). Although GnRH agonists are currently the GnRH analogue of choice for the clinical treatment of central precocious puberty, rodent studies show promising potential applications for GnRH antagonist in central precocious puberty treatment (36).

GnRH ANALOGUE UTILITY IN TRANSGENDER HORMONE THERAPY

Transgender individuals have a gender identity that differs from their sex assigned at birth. A 2016 report estimated approximately 1.4 million Americans identified as transgender (37). A transgender male (female sex at birth and male gender identity) and transgender female (male sex at birth and female gender identity) may undergo gender affirmation therapy via hormonal and/or surgical options. Hormonal therapy facilitates the development of secondary sex characteristics of the gender the person identifies with.

In the treatment of adolescents who meet the criteria for gender dysphoria, puberty may be suppressed with GnRH analogues (38). Current practices use GnRH agonists, and more information is needed to determine the potential role of antagonist therapy (38). Puberty suppression has been reported to be associated with improved depressive symptoms in adolescents with gender dysphoria. Given the potential stunting of GnRH analogues in oocyte maturation and spermatogenesis, therapy may be paused for fertility preservation if desired (38).

Gonadotropin-releasing hormone agonists are used in protocols for a transgender female for optimal antiandrogen effects and function to inhibit endogenous testosterone production (3, 38). During the gender-affirming medical treatment for a transgender male, GnRH agonists may be used to suppress ovarian hormone production. Once the testosterone levels from exogenous administration are higher enough, testosterone will inhibit the HPO axis, and GnRH agonist therapy can be stopped (3).

GnRH ANALOGUE APPLICATIONS IN CANCER AND GONADOTOXIC THERAPIES

Gonadotropin-releasing hormone analogues have been used in the treatment regimens of hormone-responsive cancers. As previously mentioned, GnRH agonists were initially used for the treatment of prostate cancer, and androgen-deprivation therapy continues to be the mainstay of treatment (39). In breast cancer treatment, gonadotropin analogues are used for ovarian suppression and autologous hormone reduction in premenopausal women diagnosed with breast cancer (40) and may be an option for ovarian suppression in women who desire future fertility. Gonadotropin-releasing hormone agonists can be employed as a tool for ovarian suppression in breast cancer therapy, either via sole use or as a bridge to oophorectomy or ovarian radiation. When used in conjunction with tamoxifen, ovarian suppression is associated with higher disease-free survival and overall survival than that when tamoxifen alone is used (41).

Moreover, GnRH agonists have become a useful tool for ovarian suppression for girls and women undergoing treatment for malignancies or autoimmune conditions. If regimens include medications known to be gonadotoxic, such as alkylating chemotherapy drugs, gonadotropin analogues may have potential benefit to reduce the risks of gonadotoxicity (3, 42). Importantly, studies with long-term outcomes of GnRH analogue function for fertility preservation are lacking (42, 43). Clinically, GnRH agonists are a useful tool to offer patients when other potential options for fertility preservation, such as cryopreservation, would otherwise delay urgent, critical treatment.

ROLE OF GnRH OUTSIDE OF THE HPO AXIS

The roles for GnRH and GnRH-R have been described in physiology outside of the HPO axis. For example, emerging literature suggests that GnRH impacts gastric motility, which may explain why some women being treated with GnRH analogues experience gastrointestinal dysmotility (44). Moreover, it is hypothesized that LH may stimulate amyloid generation associated with neurodegenerative disorders, such as Alzheimer's disease (45). The rates of neurodegenerative diseases are lower in men with prostate cancer treated with GnRH agonists, suggesting a protective mechanism for GnRH analogue therapy (45). Current clinic practice at the time of this publication do not use GnRH analogues for therapy for gastrointestinal or neurodegenerative disorders; however, ongoing research may expand of GnRH analogues to nonreproductive applications.

CONCLUSION

GnRH stimulation of the GnRH receptor regulates the entire hypothalamic, pituitary, gonadal axis. The GnRH receptor is, therefore, an ideal pharmacologic target, and its modulation via GnRH analogues grants clinicians the opportunity to treat almost any sex steroid hormone–mediated disease and control the reproductive axis in ART. Innovations initially led to the modification of the GnRH molecule to function as either agonists or antagonists. The subsequent development of orally administered small molecule inhibitors of the GnRH receptor allowed widespread applications that are already dramatically changing gynecologic practice. Gonadotropin-releasing hormone analogues have led to novel treatments and transformed care for prostate cancer, fertility, fibroids, and endometriosis.

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