Research Article

Gonadotrophine Releasing Hormone Agonist As A Trigger of Ovulation in poly cystic ovary syndrome

Emad A. Abd El-Moaty, Mohamed A. Mohamed, Mamdouh T. Hamdy, Hashem F. Mohamed and Ayman M. Yousef
Department of Obstetrics and Gynecology, Faculty of Medicine - Minia University, Egypt

Corresponding Author
Emad Ahmed Abd El-Moaty
emadabdelmoaty@gmail.com
Assistant lecturer of Obstetrics and Gynecology, Faculty of Medicine - Minia University, Egypt

Abstract
Gonadotropin-releasing hormone agonist (GnRH-a) has been used to suppress gonadotropins in several conditions including endometriosis, uterine fibroids, central gonadotropin-dependent precocious puberty, where gonadotropin suppression does not occur immediately, but there is a transient increase “flare” in sex hormone levels, followed by a lasting suppression of hormone synthesis and secretion. When using GnRH analogues to trigger ovulation, the mean concentration of LH as measured by radioimmunoassay may be actually raised although there is reduced pulsatile secretion and so the bioactive LH is markedly reduced, where the GnRH-a induced surge consists of two phases; a short ascending one (4h) and a long descending one (20 h), with subsequent induction of an FSH surge comparable with the surge of the natural cycle.

Key Words: GnRH-a; gonadotropin; radioimmunoassay; Ovulation

Introduction
Gonadotropin-releasing hormone (GnRH) was first isolated, characterized, and synthesized by Schally and Guillemin in 1971.1 However, it was the classic work by Knobil and co-workers demonstrating (1) that the pulsatile secretion of GnRH by the hypothalamus is the primary process controlling the menstrual cycle,2,3 and (2) that tonic GnRH stimulation causes down-regulation of the pituitary GnRH receptor, that led to the widespread investigation of the therapeutic potentials of GnRH. Since that time, long-acting synthetic analogues of endogenous GnRH have gained widespread use in clinical gynecology for the treatment of pelvic pathology such as leiomyomas and endometriosis and as adjunctive therapy for use in ovulation induction with gonadotropins.4

Since 1980, pulsatile GnRH has also been used with considerable success to stimulate the release of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) from the pituitary gland for clinical ovulation induction.5,6

Physiology
GnRH is a decapeptide that has been found in a number of mammals, including humans (Fig. 1). In postpubertal primates, GnRH is synthesized in the arcuate nucleus of the hypothalamus and is released in a pulsatile fashion and transported via the portal circulation to the anterior pituitary, where it stimulates the release of FSH and LH from gonadotropes. Immunohistochemical studies suggest that GnRH cells have an origin in the olfactory pit7 and migrate during early development to their final destination in the hypothalamus by approximately 11 weeks’ gestation.8 The GnRH gene sequences were first isolated in 1984,9 and the human gene was localized to the short arm of chromosome 8 (Fig. 2).10 The GnRH decapeptide results from the post-translational processing of a larger 92 amino acid polypeptide and is frequently released in tandem with the GnRH-associated peptide (GAP). GAP may play a role in prolactin regulation. GnRH is rapidly degraded in the peripheral circulation, with a half-life of 2–8 minutes.11
Several features unique to the GnRH system make its pulsatile administration for ovulation induction theoretically advantageous compared to stimulation with either clomiphene citrate or exogenous gonadotropins. First, the GnRH receptors on pituitary gonadotropes increase in response to episodic GnRH stimulation. This ‘self-priming’ function allows an enhanced LH and FSH response to a steady dose of GnRH. Second, the feedback communication between the ovary and the pituitary remains intact, thereby allowing physiologic modulation of the cycle response and decreasing the risk of ovarian hyperstimulation or multiple pregnancy. Finally, for patients in whom fertility is a concern, GnRH has no antiestrogenic effects on the endometrium, thus providing a more receptive environment for implantation.

**Indications and Patient Selection**

Ovulation induction with pulsatile GnRH has also been used in many other settings. It has been used as a therapeutic modality in women with disordered endogenous GnRH secretion, such as polycystic ovary syndrome (PCOS), hyperandrogenic anovulation, and late-onset congenital adrenal hyperplasia, who are resistant to ovulation induction with clomiphene citrate. As will be discussed below, however, ovulation and pregnancy success rates in these groups are much lower than in women with hypogonadotrophic hypogonadism. Women with anovulation secondary to hyperprolactinemia respond similarly to those with GnRH deficiency, but the relative ease of administration and efficacy of the specific dopamine agonists make hyperprolactinemia a relatively rare indication for pulsatile GnRH. More logically, GnRH has also been used with success for ovulation induction in unusual causes of hypogonadotropic hypogonadism, such as the sequelae of treatment for cranial tumors or amenorrheic lactating postpartum women.

Depending on an infertile couple’s history, documentation of tubal patency, normal uterine anatomy, and normal sperm parameters may be indicated before embarking on a course of pulsatile GnRH therapy. For women with anovulation resulting from conditions other than hypogonadotropic hypogonadism, a trial of clomiphene citrate is usually warranted before attempted ovulation induction with GnRH.

**Expected Outcomes**

For women with hypogonadotrophic hypogonadism, ovulation can be expected to occur in more than 90% of cycles (Table 1). Rates as low as 80% are reported from the earliest studies, but many of these stimulated cycles were performed with SC therapy and

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**Fig. 1.** The amino acid sequence of the decapeptide gonadotropin-releasing hormone (GnRH), first isolated, characterized, and synthesized in 1971.

**Fig. 2.** Human GnRH gene consisting of four exons located on the short arm of chromosome 8. Exon I encodes a 5’ untranslated region. Exon II encodes GnRH and includes part of GAP. Exon III encodes GAP.
suboptimal pulse frequencies. In fact, ovulatory rates are so high in women with hypogonadotropic hypogonadism, that a failure in the delivery system should be considered in those women who do not ovulate. As discussed above, ovulatory rates are much lower in women with PCOS. In a review of 600 GnRH-induced cycles, decreased success was noted in overweight patients as well as those with elevated baseline LH, testosterone, and insulin levels.

Table 1. Outcome with pulsatile GnRH therapy for ovulation induction in selected studies

<table>
<thead>
<tr>
<th>Indications</th>
<th>No. of patients</th>
<th>No. of cycles</th>
<th>GnRH dose (μg)</th>
<th>Frequency (min)</th>
<th>Route</th>
<th>Ovulatory cycles (%)</th>
<th>Pregnancy rate per ovulatory cycle (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HH, HA</td>
<td>292</td>
<td>600</td>
<td>1.25–20</td>
<td>60–120</td>
<td>IV</td>
<td>75</td>
<td>23</td>
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<td>PCOS, others</td>
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</tr>
<tr>
<td>HH, HA</td>
<td>17</td>
<td>45</td>
<td>1–10</td>
<td>60–240</td>
<td>IV</td>
<td>82</td>
<td>30</td>
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<tr>
<td>HA</td>
<td>41</td>
<td>118</td>
<td>3–15</td>
<td>60–240</td>
<td>IV</td>
<td>93</td>
<td>31</td>
</tr>
<tr>
<td>HH, HA, PCOS</td>
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<td>187</td>
<td>2.5–5</td>
<td>60</td>
<td>IV</td>
<td>76</td>
<td>32</td>
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<tr>
<td>HA</td>
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<td>20</td>
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<td>IV</td>
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<tr>
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<td>67</td>
<td>1–40</td>
<td>60</td>
<td>SC</td>
<td>96</td>
<td>28</td>
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</tbody>
</table>

One retrospective study compared exogenous gonadotropin stimulation (30 patients and 111 cycles) to pulsatile GnRH therapy (41 patients and 118 cycles) for ovulation induction in hypogonadotropic amenorrhea. Overall ovulatory rates (93% vs. 97%) and pregnancy rates per cycle (29% vs. 25%) were not significantly different between the two groups. Life-table analysis, however, revealed a higher cumulative 6-month pregnancy rate for the GnRH group (96%) than the exogenous gonadotropin group (72%). To date, no randomized clinical trial has been performed comparing the two methods of therapy, but the life-table analyses clearly reveal the therapeutic efficacy of pulsatile GnRH therapy in the select group of patients with hypogonadotropic hypogonadism.

Complications
The overall incidence of complications with GnRH therapy is low. The risk of multiple gestation with pulsatile GnRH is greater than in the general population, but lower than that seen with exogenous gonadotropin therapy and comparable to that resulting from clomiphene citrate therapy. Rates of multiple gestation resulting from GnRH cycles is in the range of 4–8%.

Mild ovarian hyperstimulation has occasionally been reported with GnRH-induced cycles, but resolves quickly upon discontinuation of the therapy, perhaps because the prolonged stimulus of exogenous hCG is rarely present. Moderate or severe ovarian hyperstimulation, however, is extraordinarily rare. This is in contrast to the reported experience with exogenous gonadotropins plus hCG with 23% of cycles resulting in mild to severe, and occasionally life-threatening, hyperstimulation syndrome.

Infectious complications are also rare, even with prolonged indwelling IV catheter placement. Superficial phlebitis at IV sites and cellulitis at the site of SC catheters have been reported. The largest prospective study to date...
followed 230 catheters for 1958 catheter days. Just 11% of all catheter tips cultured positive, and only 2% of 195 blood cultures were positive. All positive blood cultures were obtained from patients with catheters in place for only 4–7 days. No positive blood cultures were obtained from patients with 97 catheters in place for more than seven days. Two of the four positive blood cultures grew Staphylococcus epidermidis and were thought to be possible contaminants. None of the four patients with positive blood cultures were clinically ill, none received antibiotics, and three had follow-up blood cultures within 10 days, all of which were negative.22

The data suggest that the use of IV administration is associated with a low incidence of infectious complications. Nevertheless, for women with cardiac valvular disease (e.g. mitral valve prolapse) or any prosthetic device, it may be preferable to use the SC route of administration to minimize the theoretic risk of endocarditis.23

The potential of antibody formation with GnRH therapy apparently exists, but has not been extensively studied. A 3% rate of GnRH antibody formation during 3 weeks to 9 months of SC GnRH therapy in 141 men and 22 women has been reported, but the clinical significance of these findings remains unclear.24

References


