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Potential Diagnostic Utility of Intermittent Short-Acting GnRH Agonist Administration in Gonadotropin Deficiency

Carrie A. Zimmer, M.D., Ph.D., **David A Ehrmann, M.D.**, and **Robert L. Rosenfield, M.D.**[a]
Departments of Medicine and Pediatrics. Section of Adult and Pediatric Endocrinology, Diabetes & Metabolism., University of Chicago, Chicago IL 60637

Abstract

Objective—The objective was to determine if intermittent, low-dose, short-acting GnRH agonist (GnRHag) administration up-regulates pituitary-gonadal function in gonadotropin deficiency (GnD) sufficiently to be of diagnostic or therapeutic value.

Design/Intervention—Low-dose leuprolide acetate was administered SC at 4–5 d intervals up to one year.

Patients—Adult volunteers and GnD patients were studied.

Setting—The studies were performed in a General Clinical Research Center.

Main Outcome Measures—LH, FSH, and sex steroid responses were determined.

Results—In normal men and women, low-dose GnRHag repetitively transiently stimulated gonadotropins in a gender-dimorphic manner. In congenitally GnD deficient men (n=6) and women (n=1), none of whom had a normal LH response to an initial GnRHag test dose, this regimen consistently stimulated LH to the normal baseline range within two weeks. Long-term GnRHag administration to a partially GnD man did not alleviate hypogonadism, however. Women with hypothalamic amenorrhea (n=2) responded normally to a single GnRHag injection; however, repeated dosing did not seem to induce the normal priming effect.

Conclusions—The subnormal LH response to GnRHag of congenital GnD normalized in response to repetitive intermittent GnRHag, but not sufficiently to improve hypogonadism. Hypothalamic amenorrhea patients lacked the priming response to repeated GnRHag, but otherwise had normal hormonal responses to GnRHag. We conclude that intermittent administration of a short-acting GnRHag is of potential diagnostic value in distinguishing hypothalamic from pituitary causes of GnD.

Keywords

gonadotropin deficiency; gonadotropin-releasing hormone agonist; repetitive administration; gonadotropin sexual dimorphism

[a]Corresponding Author Robert L Rosenfield, MD, The University of Chicago Pritzker School of Medicine, Sections of Adult and Pediatric Endocrinology, Diabetes & Metabolism. The University of Chicago Medical Center, 5841 S Maryland Ave, MC-5053, Chicago, IL 60637, Phone: 773-702-6432 Fax: 773-702-0443, robros@peds.bsd.uchicago.edu.

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INTRODUCTION

Patients with gonadotropin deficiency (GnD) typically have subnormal gonadotropin responses to acute GnRH (1,2) or GnRH agonist (GnRHag) administration (3,4). Pulsatile GnRH administration usually corrects the gonadotropin deficiency within weeks, which indicates that they are GnRH-deficient (5). These results have not been replicated by administering GnRHag at two-day intervals (6,7), because of the GnRHag-desensitizing (down-regulating) effect on gonadotropin secretion (8), or at one-week intervals, because this is too infrequent to up-regulate gonadotropin release (9). We reasoned that a stimulatory outcome might be accomplished by developing a regimen of intermediate frequency, low-dose GnRHag administration that would avoid desensitization, yet be sufficiently frequent to prime increasing gonadotropin responses.

We here demonstrate that low-dose leuprolide (10) given at 4–5-day intervals for two weeks repetitively stimulates the pituitary-gonadal axis of normal men and women. We also show that repeated intermittent low-dose GnRHag administration results in increasing LH responsiveness that may be helpful in diagnosing hypothalamic GnRH deficiency, but lacks therapeutic potential in GnD.

METHODS

Subjects

Healthy adult male (n=39) and eumenorrheic female (n=10) volunteers, age 18 to 35 years old, were recruited by advertisement as controls. GnD males (n=6), 15 to 27 years old, were recruited from the endocrinology clinics of the University of Chicago Medical Center. Males had diagnoses of Kallmann's syndrome (n=2; relatives with KAL-1 mutation (11)), idiopathic congenital panhypopituitarism (n=2), familial hypogonadotropic hypogonadism (n=1) and idiopathic partial gonadotropin deficiency (n=1). The latter was a 24-year old male whose testes were low-normal adult size (10 cc); otherwise, all had prepubertal size testes, and all were sexually infantile with plasma testosterone <50 ng/dl, prepubertal LH and FSH levels, and azoospermia. One female GnD patient had familial hypogonadotropic hypogonadism (n=1, prepubertal 13.25-year old sibling of the above male). The others were sexually mature women with hypothalamic amenorrhea that was idiopathic (n=1; low-normal gonadotropin and estradiol levels) or secondary to chronic disease (n=1, Gitelman's syndrome; low gonadotropins and estradiol). With the exception of abnormalities mentioned above, all study subjects had unremarkable histories, examinations, and all patients had unremarkable screening tests for chronic endocrine, metabolic, or systemic disorders. Ethnicity was non-Hispanic Black 17%, non-Hispanic White 60%, Hispanic 5% and other 17%. These studies were approved by the University of Chicago Institutional Review Board and were performed after obtaining informed consent.

Study Design

Study 1 (response to single dose GnRHag in healthy volunteers)—At 0700 hr on day 1, after collecting baseline blood every 15 minutes for one hr, leuprolide acetate (GnRHag) injection was given as single dose of 1.0 or 10 μg/kg SC in random order to men in the University of Chicago General Clinical Research Center. Blood samples were then obtained at intervals up to 96 hrs after the injection for LH, FSH, and sex steroids. Women were studied similarly on 1.0 μg/kg GnRHag commencing on day 2–6 of their menstrual cycle.

Study 2 (response to repeated low-dose GnRHag in healthy volunteers)—A subset of healthy males received 1.0 μg/kg GnRHag again on days 5 and day 9. Females

(n=5) received two more doses of GnRHag at 5-day intervals. After each injection, blood was sampled at 0–4 hrs and then daily until the next injection. Pelvic ultrasound examination was performed every 2–4 days, and progesterone was evaluated at baseline and 4 days after the last injection.

Study 3 (response of GnD patients to low-dose GnRHag at 5-day intervals)— GnD males received GnRHag 1.0 μg/kg SC every 5 days for 30 days, and GnD females did so for up to 11 days. After an initial 24-hr study following the day 1 GnRHag test dose, baseline and acute (0–4 hr) hormone responses were monitored similarly to Study 2. Pelvic ultrasound was performed every 2–4 days in females.

Study 4 (therapeutic trial of prolonged repetitive GnRHag administration)— Following study 3, the one partially GnD male underwent one year of intermittent GnRHag treatment with variation of interval (4 or 5 days) and/or dose (1.0 or 10 μg/kg). Testosterone cypionate therapy, 200 mg IM every two weeks, was added on day 287 of intermittent GnRHag administration for symptomatic relief and to determine if it would enhance spermatogenesis. Hormonal response testing and testicular ultrasound examinations were performed regularly.

Laboratory and Procedural Methods

Plasma total testosterone and estradiol were measured by commercially available immunoassay kits (testosterone, Coat-A-Count, Diagnostic Products Corporation, Los Angeles, CA; estradiol, Pantex, Santa Monica, CA) (10). Progesterone was measured by radioimmunoassay after preliminary chromatography (12). LH and FSH were measured by immunochemiluminometric assay (Delphia, Wallac, Finland) (13). Real-time testicular and vaginal pelvic ultrasound imaging were performed using an Acuson Sequoia with a 4 Mhz transducer (Acuson, Mountainview, CA) and a GE Voluson 730 5–9 MHz transducer (General Electric Fairfield,CT), respectively

Data Analysis

Baseline values were computed by averaging values from the hour preceding GnRHag injection. The significance of differences among responses to GnRHag was tested by repeated measures ANOVA, after logarithmic transformation as necessary for normalization of data distribution, and between group evaluation was tested by one-way ANOVA. Post hoc evaluation was by Fisher's protected least significant differences test. Results are reported as mean±SEM, unless otherwise noted. *P* values < 0.05 were considered statistically significant.

RESULTS

Study 1. Response to Single Dose GnRHag in Healthy Volunteers (Table 1)

Men—LH peaked at 1–4 hr in 95% of subjects on the low dose, but later (24 hr) in 33% on the larger dose, at which time a statistically significant difference emerged between doses. FSH peaked at 4 hr in 60% on the lower dose and at 24 hr in 56% on the larger dose; values were significantly higher on the larger dose from 0.5–48 hr ($p<0.01$). The LH/FSH ratio at baseline was 1.3±0.13 (5^{th}–95^{th} percentile 0.35–4.3); that 4 hr post-GnRHag was 4.3±0.5 (2.0–8.3) for the 1.0 μg/kg dose and 2.5±0.4 (0.13–4.8) for the 10 μg/kg dose. Testosterone rose significantly ($p<0.0001$) at 24 hr by an average of 41±0.05% (111–190) after 1.0 μg/kg and by 53±8% (108–206%) after 10 μg/kg GnRHag; it remained significantly, but variably, above baseline at 48 hr only on the higher dose ($p<0.001$).

Women—In response to 1.0 μg/kg GnRHag LH rose significantly and steadily from 0.5 through 4 hr and then fell to a level above baseline by 24 hrs. FSH rose steadily from 0.5 hr until 4 hrs, and then fell to baseline by 24 hr. LH and FSH peaks occurred at 3–4 hr in all. LH/FSH ratio was 0.8±0.2 (0.3–1.6) at baseline and 2.8±0.4 (1.1–5.6) at 4 hr. Estradiol rose significantly at 24 hrs in response to GnRHag and returned to baseline by 48 hrs.

Comparison between sexes on 1.0 μg/kg GnRHag—LH levels were similar in both sexes at baseline, but rose faster in males so that they had significantly higher levels than females at 0.5–1 hr ($p \leq 0.002$). However, unlike men's gonadotropin levels, which plateaued, women's LH levels continued to rise, becoming significantly higher than men's at 2 hr ($p=0.02$) through 4 hr ($p=0.003$). FSH levels were significantly higher in women at baseline ($p<0.001$), and, like LH, they continued to rise so that the differences increased from 2 hr through 4 hr ($p <0.001$). By 24–48 hr, both LH and FSH fell to near baseline levels, with women's levels slightly higher at 48 hr ($p<0.005$). There was a significant difference between sexes in the LH/FSH ratio at baseline ($p=0.01$), but not at the 4-hr peak.

Study 2. Response to Repeated Low-Dose GnRHag in Healthy Volunteers (Figure 1)

Men—GnRH agonist 1.0 μg/kg dosing at 4-day intervals stimulated significant LH responses to each injection, but a significant FSH response to only the first. The peak LH decreased ($p<0.05$) with repeated administration, but the average LH over the 4-hr test interval did not. The LH/FSH ratios at baseline and peak were not changed by repeated GnRHag administration. While testosterone levels rose 24 hrs after each GnRHag injection, they dipped significantly below baseline at 3 days and then began to rebound at 4 days. This suggested that a 4-day interval might not be sufficient time for recovery of normal pituitary-gonadal responsiveness to GnRHag stimulation, so subsequent studies were carried out at 5-day intervals.

Women—GnRHag 1.0 μg/kg administered at 5-day intervals repeatedly stimulated significant, brisk, transient LH and FSH release, with unchanged LH/FSH baseline and peak ratios. Estradiol repeatedly rose 24 hr later, returned to baseline at 48 hrs, and then increased spontaneously over the subsequent 2 days after each injection. Thus, the baseline estradiol on the day of each subsequent GnRHag dose was significantly above the previous baseline. Progesterone levels at study commencement were 31±7 ng/d. In two of the five volunteers, 72–96 hr after the final dose of GnRHag, progesterone rose to 253–439 ng/dl, estradiol secondarily rose to 181–731 pg/ml, and ovarian size increased 3–8 fold in association with ovarian "cyst" development, indicating that ovulation had occurred. Dosing GnRHag at 1.0 μg/kg at 5-day intervals thus seemed optimal for further study.

Study 3. Response of GnD Patients to Low-Dose GnRHag at 5-Day Intervals (Figure 2)

Men—Congenitally GnD males had lower baseline LH (0.1–0.7 U/L) and FSH (0.15–0.6 U/L) than controls. LH rose significantly, but subnormally, after the initial dose of GnRHag, whereas FSH responses were normal in half. The LH peak successively increased with repeated dosing, quickly returning to baseline after each injection. FSH rose into the normal baseline range following the first dose of GnRHag; however, repeated administration did not significantly potentiate the FSH response. The LH/FSH ratio was 0.90±0.38 (range 0.25–2.7) at baseline and 0.65± 0.33 (0.2–2.3) 4 hrs after the first GnRHag dose; those post-GnRHag were all below normal. The peak LH/FSH ratio rose significantly by day 30 (1.3±0.4, $p < 0.05$), becoming normal in two subjects. Testosterone did not change after repeated GnRHag dosing.

Women—The congenital GnD female had low baseline (0.14 U/L) and peak (3.4 U/L) LH and low baseline (1.4 U/L) but normal peak FSH (13.5 U/L) responses. LH and FSH peaks

were slightly higher in response to the second GnRHag injection, but remained subnormal, and estradiol remained <10 pg/ml.

In contrast, the two hypothalamic amenorrhea patients responded normally to the initial GnRHag dose. The study in the subject with secondary hypothalamic amenorrhea was aborted because she developed a 3.4 cm^2 cyst in response to the first GnRHag injection. The subject with idiopathic hypothalamic amenorrhea underwent a 2-week study and repeatedly experienced brisk LH, FSH, and estradiol responses that were into the normal range. However, in contrast to normals, these responses waned with each successive GnRHag injection, and estradiol fell back to the control level each time. Her treatment was not followed by hormonal evidence of ovulation.

Study 4. Therapeutic Trial of Prolonged Repetitive GnRHag Administration (Figure 3)

The one male patient with partial GnD underwent prolonged treatment with intermittent GnRHag. By one month, LH and FSH consistently responded normally but evanescently to GnRHag. Modest testosterone responsiveness developed: levels rose from baselines of 23–28 ng/dl to 36–87 ng/dl 24-hr post-GnRHag. Repeated GnRHag administration at a variety of combinations of dose and interval resulted in only modest testosterone responses, but no semen production. The administration of testosterone did not change the gonadotropin responses to GnRHag administration, the testes did not enlarge, and the semen lacked sperm.

DISCUSSION

This study was designed to determine if GnD patients can achieve normal gonadotropin levels in response to repetitive GnRHag administration at an optimal dose and interval. First, we demonstrated in normal men and women that low-dose GnRHag administration at 4 to 5-day intervals consistently transiently stimulated gonadotropin and sex steroid levels, in a gender-specific manner. Then, in congenitally GnD men and women, none of whom had a normal LH response to an initial GnRHag test dose, we showed that this regimen consistently stimulated LH to approximate the normal baseline range within two weeks. However, long-term GnRHag administration to a partially GnD man did not further potentiate gonadotropin release sufficiently to alleviate hypogonadism. Additionally, women with hypothalamic amenorrhea, unlike congenital GnD, responded normally to a single GnRHag injection, but repeated dosing did not seem to induce a normal priming effect on follicular function.

We here confirm our earlier finding (10) that normal men and women have sexually dimorphic patterns of gonadotropin response to GnRHag administration. Most strikingly, women had a smaller early LH response, but a greater LH peak, as well as higher baseline and peak FSH than men. These data are interpretable in terms of the two-pool model of gonadotropin release (14,15), which would indicate that normal males have a larger readily releasable pool of gonadotropins than females, but females have a greater capacity to synthesize gonadotropins in response to intense GnRH stimulation, which may be what enables them to mount the mid-cycle gonadotropin surge.

The sex steroid pattern in response to repeated GnRHag administration also differed between normal men and women. After responding to each GnRHag dose, men’s testosterone levels transiently fell below baseline, suggesting Leydig cell desensitization (16,17). In contrast, women’s baseline estradiol never fell below the control level and indeed continued to climb in tandem with increasing LH responses to GnRHag; furthermore, follicular development culminated in ovulation in two women. It seems as if thecal desensitization to LH was counteracted by FSH stimulation of follicular development and

gonadotrope desensitization to GnRHag was counteracted by the positive feedback effect of the resultant estradiol secretion (18).

GnD males responded to GnRHag administration at 5-day intervals with significant potentiation of LH release, but the LH response was subnormal and transient, testosterone did not increase, and the FSH-predominance of severe GnD (9,19) persisted. One-year's treatment of a patient with partial GnD, altering the interval of GnRHag administration and varying the dosage by ten-fold, did not lead to sufficiently sustained repetitive LH and FSH responses to normalize testosterone levels or to correct azospermia. Since high intratesticular testosterone levels are important for the initiation of spermatogenesis (20,21), we attempted supplementing intermittent GnRHag therapy with replacement testosterone; however, this treatment did not improve azoospermia, as has been reported for the combination of FSH and testosterone treatment of GnD men (22). Notably, exogenous testosterone did not alter the LH or FSH response to GnRHag, which is consistent with similar studies with natural GnRH (23–25).

In contrast to the female with congenital GnD, whose responses to GnRHag resembled those of congenitally GnD males, women with hypothalamic amenorrhea had normal LH, FSH and estradiol responses to the first GnRHag test dose, as expected from such studies of GnRH itself (26,27). Although normal responses recurred with each subsequent GnRHag injection in the one hypothalamic amenorrhea patient tested repetitively, unlike normal women, she did not exhibit a self-priming effect at either the gonadotrope or the ovarian level, and her estradiol responses tended to wane with successive doses.

We conclude that intermittent GnRHag administration may be useful to distinguish hypothalamic from pituitary causes of GnD. However, it does not seem to be a promising form of treatment for hypothalamic GnRH deficiency.

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Abbreviations

GnD	gonadotropin deficiency
GnRHag	gonadotropin releasing hormone agonist

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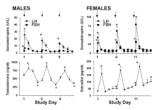

Figure 1.

Effect of repeatedly administering GnRHag (1.0 μg/kg) in healthy volunteers. GnRHag (arrows) was given at 4 (males, n=5) or 5 (female, n=5) day intervals. Peak gonadotropin responses (shown) occurred on the day of GnRHag administration. Significant differences from day 1 baseline within a group are shown (* $p<0.05$). Notice scale differences between males and females.

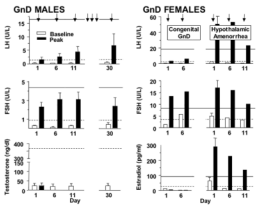

Figure 2.

Effect of repeatedly administering GnRHag (1.0 μg/kg) to GnD patients. GnRHag administration was repeated every 5 days (arrows) in both male GnD (n=6) and female GnD (n=3) patients. Testosterone was only sampled at baseline in men, while estradiol was sampled daily, with black bars representing 24 hrs after injection. Baseline and peak responses are indicated by open and closed bars, respectively. The lower limits of baseline (dotted line) and peak levels (solid line) for normal volunteers are shown for comparison. LH and estradiol responses of the congenitally GnD female patient (n=1) were low, but those of the hypothalamic amenorrhea patients (n=2) were normal. Notice scale differences between males and females.

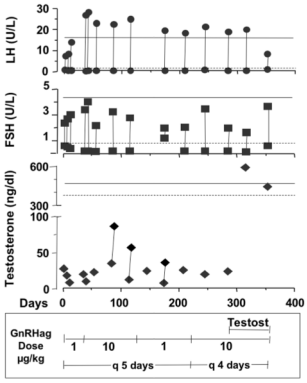

Figure 3.

Long term, intermittent GnRH agonist treatment of a partially GnD male. The response to GnRHag dose and interval variation was tested. On days 1–21 the patient was given 1.0 μg/kg GnRHag every 5 days. Between days 22–135 GnRHag dose was increased to 10 μg/kg every 5 days. For days 136–210 the patient was again given 1.0 μg GnRHag every 5 days. On day 211 through the remainder of the evaluation, the GnRHag dose was changed to 10 μg/kg every 4 days. On day 287, depot testosterone (50 mg every 2 weeks, then increased to 100 mg every 2 weeks) was added. The acute hormonal responses to GnRHag administration were tested intermittently as shown; vertical lines connect baseline and peak at each visit (the testosterone response was only evaluated at 24–48 hr on three occasions). There was no obvious effect of the testosterone supplementation on LH and FSH responses. The lower limit of baseline (dotted line) and peak levels (solid line) for normal volunteers at 1.0 μg/kg are shown for comparison.

Table 1

LH, FSH and sex steroid response to GnRH agonist administration in healthy volunteers. Mean ± SD (normal range)[a].

		Male Controls		Female Controls
		1.0 μg/kg (n=19)	**10 μg/kg (n=20)**	**1.0 μg/kg (n=10)**
LH (U/L)	Baseline	3.5 ± 1.2 (1.4–6.2)[b]	3.6 ±1.8 (1.4–6.2)[b]	4.1 ± 2.0 (2.0–7.3)
	0.5 HR	21.8 ± 8.4 (13.0–29.0)	26.3 ± 17.6 (3.8–55.5)	13.1 ± 4.6[c] (6.9–21.5)
	1 HR	24.6 ± 10.5 (16.3–35.0)	29.7 ± 19.7 (4.7–62.5)	14.0 ± 4.6[c] (7.1–20.0)
	3 HR	24.7 ± 8.7 (14.4–34.5)	22.6 ± 11.9 (5.7–40.5)	54.3 ± 29.8[c] (19.0–131)
	4 HR	26.8 ± 9.3 (16.5–39.5)	23.5 ± 13.2 (4.8–43.5)	62.7 ± 46.1[c] (19–187)
	24 HR	13.0 ± 7.3 (5.5–25.5)	21.7± 17.0 (3.0–46.8)	11.6 ± 3.9 (5.1–17.9)
	48 HR	2.5 ± 0.9[d] (1.3–3.9)	4.3 ± 2.7 (1.3–9.2)	4.3 ± 0.9 (2.7–5.5)
FSH (U/L)	Baseline	2.9 ± 1.4 (0.9–7.5)[b]	3.6 ± 1.7 (0.9–7.5)[b]	5.5 ± 1.9[c] (3.6–9.5)
	0.5 HR	4.7 ± 2.2[d] (1.6–8.7)	12.6 ± 11.6 (3.3–31.5)	7.8 ± 2.4 (5.3–12.8)
	1 HR	5.7 ± 2.8[d] (1.8–10.6)	16.3 ± 15.6 (4.8–48.0)	8.5 ± 3.8 (2.3–15.9)
	3 HR	6.7 ± 2.9[d] (2.1–12.6)	15.2 ± 12.1 (4.4–33.0)	20.4 ± 10.6[c] (6.8–38.0)
	4 HR	7.5 ± 3.1[d] (4.4–13.0)	14.8 ± 10.5 (4.5–37.0)	24.3 ± 13.7[c] (8.3–47)
	24 HR	6.2 ± 3.7[d] (1.5–12.0)	17.9 ± 16.5 (5.4–40.0)	9.9 ± 5.5 (5.2–22)
	48 HR	3.4 ± 1.7[d] (1.9–6.0)	5.6 ± 2.9 (2.8–11.2)	7.3 ± 4.6 (3.1–17)
T (male, ng/dl)[e] E2 (female, pg/ml)[e]	Baseline	630 ± 170 (368–879)[b]	548 ± 91 (368–879)[b]	35 ± 15 (23–73)
	24 HR	884 ± 249 (466–1260)	816 ± 160 (582–1045)	172 ± 85 (93–320)
	48 HR	640 ± 242 (349–1000)	762 ± 190 (366–994)	40 ± 20 (16–72)

[a] 5th to 95th percentile for males, observed range for females

[b] pooled baseline 2.5–97.5th percentile (n=39).

[c] p <0.05 between sexes for same dose

[d] p <0.05 between doses

[e] Abbreviations and conversions to SI units: testosterone (T) ng/dl x 0.0347= nmol/L; estradiol (E2) pg/ml x 3.61= pmol/L