Preservation of GHRH and GH-releasing peptide-2 efficacy in young men with experimentally induced hypogonadism

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Abstract

Background: Somatostatin (SS), GHRH, GH-releasing peptide (GHRP), and the sex-steroid milieu regulate GH secretion.

Objective: To test whether GHRH and GHRP remain effective secretagoggs in the face of short-term hypogonadism.

Design: Prospective, randomized double-blind.

Methods: Healthy young men (n = 24) received a GnRH agonist twice 3 weeks apart followed by placebo (n = 13, Pl) or testosterone (n = 11, testosterone) addback. Subjects were then given consecutive i.v. infusions of l-arginine (to restrain SS outflow) and a maximally effective dose of GHRH or GHRP-2 (to test corresponding secretagog pathways).

Results: GH secretion stimulated by l-arginine/GHRH and by l-arginine/GHRP-2 was unaffected by combined testosterone/estradiol (E2) depletion. The low testosterone/E2 milieu decreased basal (nonpulsatile) GH secretion (P = 0.038), without altering fasting pulsatile GH secretion or IGF1 or IGFBP-3 concentrations. IGFBP-1 (P < 0.0001) and abdominal visceral fat (AVF, P = 0.017) correlated negatively with fasting basal GH secretion. By contrast, IGF1 (P = 0.0012) and IGFBP-3 (P = 0.015) correlated positively with fasting pulsatile GH secretion. AVF (P = 0.0024) was a negative determinant, and IGF1 a positive determinant (P = 0.018), of GHRH-driven GH pulses. Responses to GHRP-2 were unrelated to any of these factors.

Conclusion: l-arginine/GHRP-2 appears to be an especially robust stimulus of GH secretion, since efficacy is unmodified by profound short-term hypogonadism, a range of AVF estimates, and a spectrum of IGF1, IGFBP-1, and IGFBP-3 concentrations. Whether robustness also applies to chronic hypogonadism is not known.

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Introduction

GH is secreted predominantly in discrete bursts under the supervision of GH-releasing hormone (GHRH, a 40 and 44 amino acid peptide synthesized in the arcuate nucleus), GH-releasing peptide (GHRP, of which ghrelin is the endogenous 28 amino acid prototype produced in the hypothalamus, pituitary gland, and stomach), and somatostatin (SS; a 14 amino acid sequence made in the periventricular nucleus). Pulsatile GH secretion is also regulated strongly by sex-steroid hormones (1), which exert their stimulatory effects to a large degree via SS, GHRH, and GHRP (2). Testosterone and its aromatized product, estradiol (E2), determine the amplitude and mass of GH pulses, whereas pathophysiological factors such as age, insulin-like growth factor (IGF)/1 feedback, and relative adiposity repress pulsatile GH secretion (3–5). In particular, administration of testosterone to prepubertal children and hypogonadal men enhances GH secretion after infusion of saline, l-arginine, or a maximally effective GHRP stimulus (6–9). On the other hand, the degree to which short-term testosterone or E2 deficiency affects combined secretagog actions in men is far less clear. Whereas two studies inferred that short-term pharmacological testosterone/E2 deprivation does not diminish the efficacy of GHRH infused alone (10, 11), how acute hypogonadism affects combined l-arginine/GHRH or l-arginine/GHRP drive is not known. This point is important, as infusion of l-arginine before or with a peptidyl secretagog has been employed to restrict hypothalamic release of SS (12–15). The motivation for using l-arginine is to permit inferences about the efficacies of GHRH and GHRP in a low-SS milieu (2). Thus, the present study utilizes sequential l-arginine/GHRH versus l-arginine/GHRP-2 infusions to examine their robustness to a
low-testosterone/low-E$_2$ milieu in healthy men. Secondly, we ask whether abdominal visceral fat (AVF) mass and prevailing markers of the IGF1 system influence combined-secretagog effects in this setting.

**Methods**

**Subjects**

Volunteers provided written informed consent approved by the Mayo Institutional Review Board and reviewed by the US Food and Drug Administration under investigator-initiated new drug numbers for GHRP-2 and GHRH. Exclusion criteria were exposure to psychotropic or neuroactive drugs within 1 year; body mass index (BMI) $< 18$ and more than $32.5$ kg/m$^2$; anemia (hemoglobin $< 12.8$ g/dl); drug or alcohol abuse, psychosis, depression, mania or severe anxiety; acute or chronic organ-system disease; use of testosterone, other anabolic steroids or glucocorticoids; endocrinopathy, other than primary thyroidal failure receiving replacement; nightshift work or recent transmeridian travel (exceeding three time zones within 7 days of study); acute weight change (loss or gain of $> 2$ kg in 6 weeks); allergy to administered peptides; and unwillingness to provide written informed consent.

Each subject had an unremarkable medical history and physical examination and normal screening laboratory tests of hepatic, renal, endocrine, metabolic, and hematologic function. The men reported normal sexual development and function.

**Protocol**

The study design was parallel-cohort, double-blind, and prospectively randomized. Twenty-four healthy young men (age $24 \pm 0.72$ (s.e.m.) year, BMI $25 \pm 0.91$ kg/m$^2$) received two consecutive i.m. injections of depot leuprolide acetate (3.75 mg i.m. 3 weeks apart) to deplete hypothalamic-pituitary-testicular and other anabolic steroid or glucocorticoid secretagog synergy between GHRH and GHRP-2 in these subjects. Secretagog infusions were scheduled during the time window 10–18 days. Each participant was studied twice $48$ h apart on separate mornings after a standardized 6-weeks to discharge from the CRU.

Secretagog infusions were scheduled during the time window 10–18 days. Each participant was studied twice $48$ h apart on separate mornings after a standardized evening meal and subsequent overnight fast.

Volunteers continued their usual level of daily physical activities, except the evening before and on the day of study. Subjects were admitted to the CRU before 1700 h and stayed overnight. Sleep was not monitored. Room lights were put out at 2230 h. To limit nutritional confounds, a single constant meal (vegetarian or nonvegetarian) was given in the CRU at $1800$ h the night before study comprising $12$ kcal/kg distributed as $50\%$ carbohydrate, $20\%$ protein, and $30\%$ fat. Volunteers then remained fasting, alcohol-abstinent, and caffeine-free overnight until the end of the infusion the next day.

In the CRU, catheters were placed in contralateral forearm veins at 0700 h to allow simultaneous infusion of secretagogues and blood sampling every 10 min for a total of $6$ h beginning at 0800 h. Sampling encompassed a 3-h baseline and 3-h stimulation interval. Infusions comprised $l$-arginine 30 gm delivered i.v. over $30$ min, followed immediately by i.v. bolus of either $1$ mg/kg GHRH (GEREF; Serono) or $3$ mg/kg GHRP-2 (Takeda Pharmaceuticals, Deerfield, IL, USA). The doses of $l$-arginine and both peptides are maximally stimulatory in adults (17, 18). $l$-Arginine was employed to antagonize central SS outflow (12, 13).

Blood was also withdrawn at 0800 h for later assay of serum E$_2$, testosterone, LH, FSH, IGF1, IGF-binding protein (IGFBP)-1, IGFBP-3, albumin and SHBG concentrations. Lunch was provided after sampling before discharge from the CRU.

**Hormone assays**

Serum GH concentrations were determined in duplicate by automated ultrasensitive two-site immunoenzymatic chemiluminescence assay performed on the Dxi automated system (Beckman Instruments, Chaska, MN, USA 55318). Interassay coefficient of variations (CVs) were $6.1\%$ at $0.46$ ng/ml, $4.3\%$ at $3.0$ ng/ml, $5.0\%$ at $7.2$ ng/ml, and $4.8\%$ at $13.6$ ng/ml. Intra-assay CVs were $4.7\%$ at $0.37$ ng/ml, $3.5\%$ at $2.5$ ng/ml, and $3.2\%$ at $14.8$ ng/ml. The lowest detectable GH concentration at $95\%$ confidence is 0.008 ng/ml determined by processing a six-point calibration curve, five quality controls, and ten replicates of zero calibrator in multiple assays. The GH standard was recombinant human 22 kDa GH.

E$_2$ and testosterone were measured by tandem liquid-chromatography ion-spray mass spectrometry. For E$_2$, intra-assay CVs were $18$, $3.8$, and $7.2\%$ at concentrations of $3.6$, $40$, and $297$ pg/ml (multiply by $3.68$ for pmol/l). Interassay CVs were $8.1$, $4.7$, and $4.9\%$ at $16$, $31$, and $119$ pg/ml respectively. For testosterone, the analytic range is $7$–$2000$ ng/dl (multiply by $0.0347$ for nmol/l) for a $0.1$ ml volume. Intra-assay CVs were $3.3$, $2.8$, $2.2$, and $2.0\%$ at testosterone concentrations of $16$, $64$, $184$, and $927$ ng/dl respectively. Corresponding interassay CVs were $5.1$, $3.8$, $3.7$, and $2.8\%$. Free and bioavailable testosterone concentrations were calculated as described earlier (19).

IGFBP-1, IGFBP-3, and total IGF1 concentrations were quantified by IRMAs (Diagnostic Systems Laboratories, Webster, TX, USA) as described (20). Intra- and interassay CVs were $6.1$ and $8.4\%$ for IGFBP-1, and $5.8$ and $8.5\%$ for IGFBP-3 respectively. Intra-assay CVs for IGF1 were $3.4\%$ at $9.4$, $3\%$ at $55$, and $1.5\%$ at $264$ ng/ml, and interassay CVs $9\%$ at $64$ ng/ml and $6.2\%$ at $157$ ng/ml.
**Statistical analysis**

An unpaired Student’s t-test was used to compare age, BMI, and AVF as well as baseline fasting hormone concentrations in the two groups. Two-way ANOVA (2×2 factorial design) was used to examine the individual and interactive effects of normal versus low testosterone/E₂ (two factors) and secretagog type (two factors) on the summed mass of GH secreted in pulses over the 3 h after secretagog infusion. *Post hoc* contrasts were made via Fischer’s least-significant difference test (21). Log transformation was used to limit the dispersion of residual variance. Linear regression analysis and Pearson’s correlation coefficient *P* value were applied to examine the relationship between GH secretion and age, AVF, IGF1, IGFBP-1, and IGFBP-3 concentrations (Systat, Point Richmond, CA, USA). Bonferroni correction was applied to the three IGF-related measures (*P* ≤ 0.0167). Significant differences were corroborated by the non-parametric rank-sum and Kruskal–Wallis tests (21).

Data are presented as the mean ± s.e.m. Experiment-wise *P* < 0.05 was construed as statistically significant.

**Statistical power analysis**

Data from 18 studies in hypogonadal or normal males (n=149 subjects total) indicate that parenteral testosterone supplementation increases mean GH concentrations by a weighted-mean effect size (SDS) of 1.8 (6, 8, 9, 11, 22–26). Power analysis assumed that testosterone/E₂ depletion exerts an opposite effect of similar relative magnitude. If comparison is made via a one-tailed (based upon the prior hypothesis) unpaired Student’s t-test at protected *P* ≤ 0.01, then analysis of data from a total of 24 subjects (~12 in each group) would achieve >99% power to detect this effect size.

**Deconvolution analysis**

GH concentration time series were analyzed using a recently developed automated deconvolution method, which was verified mathematically by direct statistical proof and validated empirically by hypothalamic-pituitary sampling and simulated pulsatile time series (27, 28). The Matlab-based algorithm first detrends the data and normalizes concentrations to the unit interval (0, 1). Second, the program creates multiple sets of potential pulse times via an incremental smoothing process (a nonlinear adaptation of the heat-diffusion equation). Third, a maximum-likelihood estimation method calculates all secretion and elimination parameters for each of the multiple candidate pulse-time sets. Deconvolution parameters comprise basal secretion (β₀), two half-lives (α₁, α₂), secretory-burst

**Figure 1** Significant hormonal differences in young men given leuprolide plus placebo versus leuprolide plus testosterone addback.

**Figure 2** Time profiles of GH concentrations sampled every 10 min for 6 h fasting in 13 young men given leuprolide and placebo (Pl) and 11 others given leuprolide and testosterone injections. Saline was infused i.v. for 3 h, then L-arginine for 0.5 h (single arrows) followed by bolus GHRH or GHRP-2 (double arrows). Data are the mean ± s.e.m.
mass \((\eta_0, \eta_1)\), random effects on burst mass \((\sigma_\lambda)\), procedural/measurement error \((\sigma_e)\), and a three-parameter flexible Gamma-secretory-burst waveform \((\beta_1-\beta_3)\). The fast half-life of GH was represented as 3.5 min constituting 37% of the decay amplitude and the slow half-life as 20.8 min (29). The Akaike information criterion (30) is used to select the optimal pulse-time set from the multiple candidate sets. Other parameters are basal and pulsatile secretion rates (concentration units/3 h), mass secreted per burst (concentration units), and waveform mode (time delay to maximal secretion after burst onset).

**Visceral fat mass**

Intraabdominal visceral fat mass was estimated by single-slice abdominal CT scan at L3–L4, exactly as reported (4).

**Results**

As described earlier and in a Supplemental (Appendix) Table, which can be viewed online at http://www.eje-online.org/supplemental/ baseline subject characteristics did not differ in volunteers assigned to the leuprolide/placebo (Pl) and leuprolide/testosterone treatment groups (16). By contrast, post-leuprolide versus post-Pl hormone concentrations differed significantly with respect to: a) IGFBP-1 (higher in the testosterone addback group, \(P=0.027\)); b) prolactin (higher in the testosterone group, \(P=0.001\)); c) FSH (lower in the testosterone group, \(P<0.001\)); and d) E2, total testosterone, bioavailable testosterone, and free testosterone (each higher by \(P<0.001\) in the testosterone group; Fig. 1). The data suggest that eugonadal testosterone concentrations contribute to maintaining IGFBP-1 and prolactin concentrations, and in suppressing FSH concentrations. IGF1, IGFBP-3, SHBG, and LH concentrations were similar in the Pl and testosterone cohorts after leuprolide injection, whereas FSH was lower after leuprolide plus testosterone \((0.35 \pm 0.11 \text{ IU/l})\) than leuprolide plus PI \((2.3 \pm 0.43 \text{ IU/l}, P=0.001)\). Therefore, testosterone potentiated suppression of FSH by leuprolide, without further affecting LH or SHBG. Moreover, IGF1 and IGFBP-3 were not affected.

**Figure 2** presents GH concentrations (mean ± S.E.M.) sampled every 10 min for 6 h, comprising 3-h saline-infused and 3-h secretagog-stimulated profiles. Data were obtained after leuprolide injection plus PI versus testosterone addback. The peak and time course of GH responses were comparable visually in the two cohorts. Unstimulated (pre-secretagog) mean GH concentrations were 0.61 ± 0.19 (Pl) and 1.3 ± 0.49 µg/l (testosterone) \((P=0.046)\), and estimated basal (non-pulsatile) GH secretion rates were 2.3 ± 0.52 (Pl) versus 4.0 ± 0.94 µg/l per 3 h (testosterone) \((P=0.038)\). Unstimulated fasting pulsatile GH secretion was not affected by the sex-steroid milieu \((P=0.37; \text{ Table 1})\). Thus, short-term testosterone depletion mainly reduced basal GH secretion. In relation to sequential secretagog-stimulated GH release, two-way ANOVA identified a

**Table 1** Impact of testosterone/estradiol (E2) depletion versus repletion on GH secretion.

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Leuprolide ± PI ((n=13))</th>
<th>Leuprolide ± testosterone ((n=11))</th>
<th>(P) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal (nonpulsatile) GH secretion</td>
<td>2.3 ± 0.52</td>
<td>4.0 ± 0.94</td>
<td>0.019</td>
</tr>
<tr>
<td>Unstimulated pulsatile GH secretion</td>
<td>5.1 ± 2.6</td>
<td>4.9 ± 1.6</td>
<td>&gt;0.10</td>
</tr>
<tr>
<td>L-arginine/GHRH stimulation</td>
<td>117 ± 19</td>
<td>103 ± 15</td>
<td>&gt;0.10</td>
</tr>
<tr>
<td>L-arginine/GHRP-2 stimulation</td>
<td>235 ± 27</td>
<td>273 ± 41</td>
<td>&gt;0.10</td>
</tr>
</tbody>
</table>

Data are the mean ± S.E.M. \(P\) values were estimated by an unpaired one-tailed Student’s t-test under the prior hypothesis that testosterone/E2 depletion lowers GH output.

*Units are µg/l per 3 h.

Figure 3 presents GH concentrations (mean ± S.E.M.) sampled every 10 min for 6 h, comprising 3-h saline-infused and 3-h secretagog-stimulated profiles. Data were obtained after leuprolide injection plus PI versus testosterone addback. The peak and time course of GH responses were comparable visually in the two cohorts. Unstimulated (pre-secretagog) mean GH concentrations were 0.61 ± 0.19 (Pl) and 1.3 ± 0.49 µg/l (testosterone) \((P=0.046)\), and estimated basal (non-pulsatile) GH secretion rates were 2.3 ± 0.52 (Pl) versus 4.0 ± 0.94 µg/l per 3 h (testosterone) \((P=0.038)\). Unstimulated fasting pulsatile GH secretion was not affected by the sex-steroid milieu \((P=0.37; \text{ Table 1})\). Thus, short-term testosterone depletion mainly reduced basal GH secretion. In relation to sequential secretagog-stimulated GH release, two-way ANOVA identified a

![Figure 3](https://example.com/figure3.png)

**Figure 3** Regression of unstimulated basal (nonpulsatile) GH secretion rates on CT-estimated abdominal visceral fat (AVF) and serum IGFBP-1 concentrations in 24 young men treated with leuprolide and PI (open circles) or testosterone (closed circles). Two-tailed \(P\) values are given with the correlation coefficients.
strong effect of L-arginine/GHRP-2 over L-arginine/GHRH (P<0.001), but no effect of testosterone versus Pl addback (P=0.79) and no interaction between secretagog and sex-steroid milieu (P=0.49). The effect of L-arginine combined with GHRP-2 on pulsatile GH secretion was 2.0- and 2.7-fold that of L-arginine/GHRH under low testosterone and high testosterone respectively. Unpaired statistical comparisons of pulsatile GH secretion (µg/l per 3 h) in the Pl versus testosterone-addback cohorts during the separate infusion of L-arginine/GHRH and L-arginine/GHRP-2 confirmed no differences due to testosterone/E2 availability for either secretagog (Table 1).

Lack of statistical difference (at good statistical power, here >95%) between Pl and testosterone-addback responses permitted combining the data (n=24 subjects) statistically (21). Linear-regression analyses in the combined cohorts revealed that basal (nonpulsatile) GH secretion was inversely related to AVF (R²=0.23, P=0.017) and directly to IGFBP-1 concentrations (R²=0.53, P<0.0001; Fig. 3). Fasting unstimulated (saline-infused) pulsatile GH secretion correlated positively with IGF1 (R²=0.39, P=0.0012) and IGFBP-3 (R²=0.25, P=0.015) concentrations (Fig. 4). These outcomes point to potentially different modulation of basal versus pulsatile GH secretion in the unstimulated fasting state. These results remained significant at Bonferroni-restricted P≤0.0167 for assessment of the three IGF-related measures.

In the setting of secretagog infusions, regression analysis revealed a markedly negative effect of AVF (R²=0.35, P=0.0024) on L-arginine/GHRH’s stimulation of pulsatile GH secretion: Fig. 5 (top). By contrast, stimulation by L-arginine/GHRP-2 was not influenced by either age or AVF (both P>0.10). There was a strong trend toward IGF1 being a positive statistical determinant of pulsatile GH secretion driven by sequential L-arginine/GHRH infusion (R²=0.23, P=0.018; Fig. 5 (bottom)). On the other hand, none of IGF1, IGFBP-1, or IGFBP-3 concentrations, age, or AVF correlated with GH responses to L-arginine/GHRP-2. Accordingly, AVF is a major negative determinant of GHRH but not GHRP-2 action in this setting.

The waveform (time-dependent shape) of GH secretory bursts is estimated as the analytical mode of the secretory burst. Instead of being a measure of mass (amount of GH released), the mode denotes the time in min to attain maximal secretion after objectively estimated burst onset. By linear regression analysis and in the case of L-arginine/GHRH infusion only, AVF (R²=0.26, P=0.011) correlated negatively, and IGFBP-1 positively (R²=0.27, P=0.0094), with GH secretory-burst mode (Fig. 6). Thus, the shape (waveform) of GH secretory events is influenced in
some manner by AVF and IGF1, but not only when the secretagog is GHRH, thereby illustrating a further distinction in the mode of action of GHRH and GHRP-2.

**Discussion**

The present study affirms with high statistical power the *a priori* hypothesis that GH responses to sequential L-arginine/GHRH and L-arginine/GHRP-2 infusions are resistant to marked short-term reduction of testosterone and E2 concentrations. The outcomes indicate that L-arginine infusion followed by either GHRH or GHRP-2 constitutes an effective secretagog combination in acutely (within 1 month) hypogonadal men. On the other hand, only sequential L-arginine/GHRP-2 also stimulated GH secretion independently of AVF and IGF markers. Thus, L-arginine/GHRP-2 may be a useful secretagog pair under clinical conditions in which hypogonadism is of recent onset and/or possible over-weightness exists.

The gold-standard insulin-tolerance test has some practical limitations, thus prompting evaluation of other powerful GH-releasing agents, such as the combination of L-arginine and GHRP-2 assessed here. For clinical utility, efficacy (maximal response) has been the conventional endpoint. However, complete dose–response estimates would be required to quantify potency and sensitivity as well. Maximal hormone concentrations (height of peak) in general correlate directly with the mass of hormone secreted per burst (31). Thus, responses to the secretagog(s) utilized here yielded consistent inferences for secretory-burst mass (Tables and Figures) and maximal GH peak height (not shown).

The leuprolide–clamp paradigm also demonstrated that – independently of testosterone/E2 status – unstimulated basal (nonpulsatile) GH secretion was determined positively by IGFBP-1 concentrations and negatively by AVF, whereas unstimulated pulsatile GH secretion was related positively to both IGF1 and IGFBP-3 concentrations. IGF1 concentrations also represented a strongly positive predictor, and AVF a strongly negative predictor, of L-arginine/GHRH efficacy. In contradistinction, none of these factors influenced L-arginine/GHRP-2 stimulation in this cohort of 24 individuals. More studies will be required to assess the generality of this inference in other cohorts.

A parsimonious explanation for the observed non-steroidal determinants of GHRH efficacy could be that high GHRH receptor–effector function enhances pulsatile GH output, which increases IGF1 and IGFBP-3 concentrations and decreases AVF. This scenario could explain both the positive association between pulsatile GH secretion and IGF1 and IGFBP-3 concentrations, and the negative association between pulsatile GH secretion and AVF. The precise reasons why GHRP does not exhibit the same multiple interdependencies with AVF- and IGF-related factors as GHRH are not so clear. A main difference from GHRH is that ghrelin/GHRP exerts hypothalamic effects required for synergism with GHRH (2).

Sex-steroid hormones in women regulate not only the amount of GH secreted in bursts, but also the waveform or time pattern of GH released within individual bursts (32). We could not detect testosterone/E2 effects on secretory-burst shape in men. The mode represents a shape- or time-sensitive estimate of the delay to maximal secretion. This waveform term is independent of the amount (mass) of hormone secreted (33). However, AVF (negatively) and IGFBP-1 (positively) correlated with the time delay to maximal GH secretion under L-arginine/GHRH drive. Analyses using atomic-force microscopy indicate that GH-containing vesicles in pituitary cells must fuse with membrane pores to allow exocytosis (34). How AVF and IGFBP-1 modulate these processes is unknown.

Little is known about the regulation of basal (nonpulsatile) GH secretion (1). In the present study, this measure correlated positively with IGFBP-1 concentrations ($R^2=0.53$, $P<0.0001$). The precise basis for this new association is not known. One plausible mechanism linking IGFBP-1 and basal GH secretion would be free IGF concentrations, which appear to inhibit GH secretion (35).
Caveats include the relatively small cohort studied (n = 24), possible unknown effects of leuprolide per se, and the need to eventually extend paradigm duration.

In summary, L-arginine/GHRH and L-arginine/GHRP-2 are robust stimulators of GH secretion in a short-term hypogonadal setting. L-arginine/GHRH efficacy is negatively determined by AVF and positively by IGF1 concentrations. No such effects were evident for L-arginine/GHRP-2 stimulation. AVF and IGFBP-1 are significant covariates of the waveform duration of L-arginine/GHRH (but not L-arginine/GHRP-2)-induced GH secretory bursts. The present outcomes delineate new distinctions between GHRH and GHRP actions, which may influence the choice of optimal secretagog in a particular clinical setting.

Declaration of interest
There is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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