CLINICAL STUDY

Amplified and orderly growth hormone secretion characterizes lean adolescents with polycystic ovary syndrome

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Abstract

Objective: The present study evaluated the hypothesis that pulsatile GH secretion is altered in adolescents with polycystic ovary syndrome (PCOS).

Design and patients: Thirteen adolescent girls with PCOS (ages 13–19 years) and ten eumenorrheic controls (ages 14–19 years) matched for a range of body mass index (BMI) values underwent blood sampling every 20 min for 12 h overnight.

Methods: Serum concentrations of GH and LH were measured by specific immunofluorometric assays (IFMA). Pulsatile secretion was quantitated by deconvolution analysis and pattern orderliness by the approximate entropy (ApEn) statistic. Fasting serum androstenedione, testosterone, 17-hydroxyprogesterone, estrone, estradiol, insulin and IGF-I concentrations were measured by RIA, GH-binding protein (GHBP) by IFMA and IGF-binding protein (IGFBP)-1 and IGFBP-3 by IRMA.

Results: Twelve-hour mean and integrated GH concentrations, the mass of GH secreted per burst, and the GH pulse frequency were not distinguishable in patients with PCOS and controls as a whole. Subanalysis of non-obese (BMI < 25 kg/m²) PCOS and healthy volunteers disclosed elevated 12-h GH production rates ($P = 0.03$) and integrated serum GH concentrations ($P = 0.04$) in (lean) patients with PCOS. ApEn analysis of the orderliness of GH release showed remarkably more regular GH secretion patterns (lower ApEn of GH release) in girls with PCOS compared with controls ($P = 0.02$). Serum GHBP, IGF-I and IGFBP-3 concentrations were similar in both groups, whether lean or obese. However, IGFBP-1 levels were lower in the combined group of PCOS subjects compared with BMI-matched controls ($P < 0.05$). In volunteers with PCOS, mean (12-h) serum GH concentrations correlated positively with mean serum LH levels ($P = 0.006$). Based on deconvolution analysis, the 12-h production rate and the mass of GH secreted per burst also correlated strongly with the cognate LH measure (both predicted) ($P = 0.004$) in PCOS. Androstenedione levels were also related to the 12-h GH secretion rate ($P = 0.02$).

Conclusions: This study shows that non-obese adolescents with PCOS secrete GH at a higher rate and with more orderly patterns, resembling a male profile. Determining whether this pattern reflects an intrinsic hypothalamic abnormality or is secondary to androgen excess in PCOS will require further studies.

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Introduction

The nature and role of disruption of the growth hormone (GH)/insulin-like growth factor (IGF) axis in the pathophysiology of polycystic ovary syndrome (PCOS) remain uncertain. Studies of GH pulsatility in PCOS are scanty and restricted mainly to the adult (1–5). Kazer *et al.* (1) reported decreased serum GH and normal IGF-I concentrations in women with PCOS compared with controls even when body mass index (BMI) was taken into account. Prèlevic *et al.* (4)

observed higher GH levels in non-obese than obese patients with PCOS or normal controls with similar plasma IGF-I concentrations among all three groups. Morales *et al.* (5) demonstrated that lean women with PCOS generate 30% higher amplitude serum GH concentration peaks than BMI-matched controls, but found no alterations in IGF-I, GH-binding protein (GHBP) and IGF-binding proteins (IGFBP).

Folliculogenesis in PCOS is marked by an accumulation of small antral follicles, and impaired progression to a dominant preovulatory follicle (6). Inasmuch as

normal ovarian cyclicity is controlled jointly by gonadotropins and intraovarian growth factors, abnormalities in one or both regulatory systems may play a role in disrupted follicle maturation in PCOS (7–9).

IGF-I and insulin amplify the *in vitro* actions of luteinizing hormone (LH) on the biosynthesis of androgens by theca–interstitial cells (10, 11). In addition, GH can upregulate the intraovarian production of IGF-I (12). The relevance of these findings is suggested by the clinical observation that patients with isolated GH deficiency or tissue insensitivity to GH (Laron syndrome) typically manifest delayed puberty. This delay is ameliorated by GH or IGF-I replacement therapy (13, 14). Some but not all clinical trials also report that GH supplementation reduced the total dose of menopausal gonadotropins required for induction of ovulation (15, 16). These ensemble observations suggest important relationships between the GH–IGF-I and hypothalamo–pituitary–ovarian axes, albeit via mechanisms that are poorly understood.

The present investigation was designed to appraise pulsatile and pattern-dependent GH secretion in adolescents with PCOS using an ultrasensitive GH assay, frequent blood sampling, deconvolution analysis to calculate GH secretory properties and the approximate entropy (ApEn) statistic to assess the orderliness of GH release. Thereby, we have unmasked a positive relationship between GH and LH or androstenedione production in (non-obese) adolescents with PCOS.

Patients and methods

Subjects

Thirteen adolescent girls with PCOS (aged 13–19 years) and ten eumenorrheic controls (aged 14–19 years) were studied. None of the subjects was hypertensive, or had evidence of Cushing's disease, drug-induced hirsutism, hyperprolactinemia or thyroid disease. Subjects had not been taking any medication (including contraceptive pills) for at least 3 months before the study. The diagnosis of PCOS was based on the following criteria: (a) clinical signs of hyperandrogenism (hirsutism, evaluated by a Ferriman–Gallwey score of at least 9 and/or acne) (17), (b) perimenarcheal onset of oligomenorrhea or amenorrhea, and (c) elevated serum levels of androstenedione and/or testosterone. In PCOS patients, late-onset congenital adrenal hyperplasia was excluded by a normal serum 17-hydroxyprogesterone (17-OHP) concentration measured 60 min after adrenocorticotropin stimulation (18). The protocol of this study was approved by the Ethical Committee of Ricardo Gutiérrez Children's Hospital and written informed consent was obtained from each subject and her parents.

The study design was as described earlier (19). Briefly, blood was sampled every 20 min for 12 h

overnight in normally cycling controls and PCOS adolescents. Seven PCOS patients presenting with oligomenorrhea and all controls were studied in the early follicular phase of the menstrual cycle (days 3–5), and the remaining six PCOS patients presenting with amenorrhea were studied on a random day at least 6 weeks after the last menses.

Assays

Serum GH concentrations were assayed in duplicate using a specific 22 kDa immunofluorometric (IFMA) method (Delfia; Wallace, Turku, Finland). Intra- and interassay coefficients of variation were 4.8% and 9.5% respectively, and the detection limit was 0.01 µg/l. All samples from a particular subject were analyzed in the same assay. Total IGF-I was measured after acid–ethanol extraction by radioimmunoassay (RIA) and IGFBP-3 and IGFBP-1 were determined by a commercial IRMA kit (Diagnostics Systems Laboratories, Webster, TX, USA).

Serum GHBP concentrations were measured by a time-resolved IFMA, as described by Fisker and colleagues (20), with some modifications. The principle of the assay is to saturate all GHBP in serum with GH, and trap the complex with an immobilized antibody against GH. The total complex is then detected by an Eu³⁺-labeled antibody against human GHBP (MAb 263; Agen, Acacia Ridge, Australia). The assay was performed using 96-well microtiter plates from the GH-Delfia Kit, coated with a monoclonal GH antibody. The antibody against human GHBP (MAb 263) was labeled using an europium-labeling kit (Delfia; Wallace) according to the manufacturer's instructions. Standards were recombinant human GHBP (DSL-R01625; Diagnostics Systems Laboratory) diluted in Delfia assay buffer. The detection range in this assay was 0.25–13 nmol/l and the intra- and interassay coefficients of variation were 7.5% and 12.5% respectively.

Serum concentrations of LH and follicle-stimulating hormone (FSH) were assayed in duplicate by IFMA as described earlier (19). Serum concentrations of insulin, 17-OHP, testosterone, androstenedione, 17β-estradiol and estrone were determined by RIA, and sex hormone-binding globulin (SHBG) by saturation analysis using tritiated 5α-dihydrotestosterone on 0700 h fasting samples, as previously described (21).

Data analysis

GH profiles in both PCOS and controls were appraised by deconvolution analysis, in which admixed basal and pulsatile hormone secretion rates were estimated concurrently via a multistep iterative fitting procedure, as described previously (22).

ApEn is a model-independent regularity statistic developed to quantify the orderliness of sequential measures, such as hormonal time series. Larger ApEn

values correspond to greater randomness (irregularity) of hormone release patterns (23).

Statistical analysis

Log-transformed data were analyzed by an unpaired two-tailed unequal-variance Student's *t*-test. Correlations between the characteristics of spontaneous GH and LH secretion and serum concentrations of sex steroids were made by simple linear regression analysis.

Results

The clinical and hormonal data of patients with PCOS and the eumenorrheic controls are summarized in Table 1. The two groups were similar in chronological and gynecological age ($P = \text{not significant (NS)}$) and BMI (range: PCOS, 18.6–35 kg/m²; controls, 19–29.5 kg/m²). However, four of the thirteen PCOS and three of the ten control adolescents showed a BMI higher than 25 kg/m². The LH/FSH ratio was markedly increased ($P < 0.001$), and serum 17-OHP, androstenedione, testosterone, and estrone concentrations were significantly elevated in PCOS over corresponding controls. Estradiol values were similar in PCOS and control adolescents. PCOS exhibited a significant decrease in SHBG concentrations ($P < 0.01$). Fasting insulin serum levels were higher in PCOS than controls ($P < 0.05$). No difference in fasting insulin levels was observed when only lean PCOS patients and controls were compared. PCOS adolescents showed a tendency to have higher homeostasis model assessment (HOMA) values than controls ($P = 0.09$). Nevertheless, no significant differences could be detected in insulin sensitivity assessed by HOMA when only lean PCOS and controls were compared (control, 2.3 ± 0.2 vs PCOS, 2.9 ± 0.36).

Pulsatile characteristics of GH secretion

Deconvolution analysis showed that basal GH secretion was similar in PCOS ($0.005 \pm 0.001 \mu\text{g/l}$) and controls ($0.003 \pm 0.0009 \mu\text{g/l}$; $P = \text{NS}$). The half-duration of GH secretory bursts (PCOS, 34 ± 2.9 ; control, 30 ± 4.2 min, $P = \text{NS}$) and the GH half-life (PCOS, 14 ± 1.1 ; control, 17 ± 1.1 min, $P = \text{NS}$) were also comparable in both groups.

Deconvolution analysis of episodic GH secretion in two eumenorrheic controls and two PCOS patients is shown in Fig. 1. Both Fig. 1A panels show data from a representative lean girl in each group and the B panels results from an obese girl with PCOS and the corresponding control. The continuous curves through the serum GH concentration profiles (Fig. 1 upper) represent the calculated reconvolution fits predicted by the multiple-parameter convolution method. Figure 1 (lower) illustrates the corresponding computer-resolved underlying GH secretory rate plotted against time.

As shown in the upper panels of Fig. 2, the mean serum GH concentration, the mass of GH secreted per burst, and the GH pulse frequency were similar in PCOS adolescents and controls. The pulsatile production rate (the product of the mean mass of hormone secreted per pulse and the number of pulses secreted per day) showed a tendency toward higher values in PCOS (Fig. 2, bottom left) ($P = 0.08$). The integrated GH concentration was similar in PCOS and control groups (Fig. 2, bottom middle) ($P = \text{NS}$).

To quantify the orderliness of GH release, we used the ApEn statistic method. As shown in Fig. 2 (bottom right), PCOS adolescents exhibited greater orderliness (lower ApEn) of GH release patterns than controls ($P = 0.02$).

When only data from lean PCOS ($n = 9$) and lean controls ($n = 7$) were taken into account, PCOS subjects showed a higher pulsatile GH production rate ($P = 0.032$) and a higher integrated serum GH concentration ($P = 0.04$) (Table 2). In addition,

Table 1 Clinical and biochemical characteristics of normal adolescents and patients with PCOS. Values are means $\pm$ S.E.M.

	Controls ($n = 10$)	PCOS ($n = 13$)
Chronological ages (years)	16.5 ± 0.5	16.4 ± 0.6
Gynecological age (years post-menarche)	4.0 ± 1.0	4.8 ± 0.4
BMI (kg/m ²)	22.3 ± 1.0	24.3 ± 1.6
LH/FSH ratio	0.66 ± 0.08	$2.47 \pm 0.4^*$
17-hydroxyprogesterone (ng/ml)	0.57 ± 0.1	$1.52 \pm 0.3^*$
Androstenedione (ng/ml)	1.25 ± 0.1	$2.49 \pm 0.3^*$
Testosterone (ng/ml)	0.45 ± 0.07	$1.45 \pm 0.2^*$
Estrone (pg/ml)	12 ± 1.4	$33 \pm 4.0^*$
Estradiol (pg/ml)	42 ± 4.2	48 ± 3.4
SHBG (nmol/l)	44 ± 4.2	$23 \pm 3.3^*$
Insulin (mIU/l)	13 ± 1.4	$22 \pm 4.0^\dagger$
HOMA	2.58 ± 0.33	4.4 ± 1.12

* $P < 0.05$, $^\dagger P = 0.05$ vs control.

SHBG, sex hormone-binding globulin; HOMA, homeostasis model assessment.

Figure 1 Individual profiles of episodic GH secretion estimated by deconvolution analysis. Twelve-hour serum GH concentration time-series were obtained by sampling blood every 20 min overnight in 13 PCOS and 10 normal girls. Panels A represent patients and controls with a BMI less than 24 kg/m² and panels B signify PCOS and controls with a BMI more than 25 kg/m². Continuous curves through the observed serum GH concentration data define deconvolution-predicted fits (upper panels). Corresponding GH secretion rates over time are based on a composite model of basal and pulsatile GH secretion (lower panels).

Figure 2 Individual values (and mean $\pm$ S.E.M.) of the episodic GH secretion estimated by deconvolution analysis, and quantification of the orderliness (ApEn) within 12-h serum GH concentration time-series obtained in 13 PCOS (PCO) and 10 normal girls. Solid circles (●) represent patients and controls with a BMI less than 24 kg/m^2 and open circles (○) signify PCOS and controls with a BMI more than 25 kg/m^2 . Mean serum GH levels, mass of GH secreted per burst, GH pulse frequency, GH production rate, and the integrated GH concentration were similar between PCOS and controls (P , not significant). PCOS patients exhibited a more orderly GH release ($P = 0.02$) than controls.

Table 2 Measures of GH secretion in lean controls and lean PCOS adolescents. Values are means $\pm$ S.E.M.

	Lean controls ($n = 7$)	Lean PCOS ($n = 9$)	P
Mean serum GH concentration (µg/l)	1.22 ± 0.14	1.69 ± 0.27	NS
Mass of GH secreted per burst (µg/l)	6.47 ± 1.23	9.19 ± 1.47	0.06
Integrated GH concentration (µg/l per min)	885 ± 101	1228 ± 194	0.04
Pulsatile production rate (µg/l per 12 h)	32 ± 4.8	48 ± 6.5	0.032
Pulse frequency (pulses/12 h)	5.3 ± 0.51	5.4 ± 0.47	NS
ApEn (1,20%)	0.64 ± 0.02	0.53 ± 0.02	0.006

NS, not significant.

Table 3 Levels of GH-binding protein (GHBP), IGF-I and IGF-binding proteins (IGFBP). Values are means $\pm$ S.E.M.

	Controls		PCOS	
	All group ($n = 10$)	Lean ($n = 7$)	All group ($n = 13$)	Lean ($n = 9$)
GHBP (nmol/l)	5.4 ± 0.35	5.2 ± 0.28	5.6 ± 0.44	4.8 ± 0.27
IGF-I (µg/l)	299 ± 25	313 ± 31	327 ± 34	333 ± 35
IGFBP-3 (mg/l)	3.1 ± 0.36	3.3 ± 0.45	3.4 ± 0.33	3.6 ± 0.36
IGFBP-1 (µg/l)	$24 \pm 6.60^*$	21 ± 6	$9.9 \pm 3.30^*$	11.3 ± 4.50

* $P < 0.05$ vs controls.

PCOS patients tended to have a higher mass of GH secreted per burst than controls of similar BMI (Table 2, $P = 0.06$). Lean PCOS patients also exhibited a remarkable increase in the orderliness of GH release compared with lean control adolescents ($P = 0.006$).

Figure 3 Linear regression analysis of (12-h) mean serum GH concentrations vs mean LH concentrations (top), LH pulse mass (middle) and LH production rate (bottom) in PCOS (●) and eumenorrheic adolescents (○). In girls with PCOS, mean serum GH concentrations correlated positively with mean LH concentrations ($r = 0.75$, $P = 0.006$), the mass of LH secreted per burst ($r = 0.77$, $P = 0.002$) and the 12-h LH production rate ($r = 0.73$, $P = 0.005$).

GHBP

As shown in Table 3, plasma concentrations of GHBP were unaltered in PCOS. GHBP levels were related positively and significantly to BMI for the combined group (PCOS and controls) ($r = 0.51$, $P = 0.02$), as well as for PCOS patients considered separately ($r = 0.66$, $P = 0.02$). GHBP levels correlate significantly and inversely with mean GH concentration ($r = -0.68$, $P = 0.015$) only in the PCOS group.

IGF-I and IGFBPs

Mean serum concentrations of IGF-I and IGFBP-3 were similar in controls and PCOS (Table 3). This was also true when only lean PCOS and controls were compared. The ratio IGF-I/IGFBP-3 was also similar in PCOS and controls.

Plasma IGFBP-1 levels were markedly lower in PCOS adolescents than controls. Although lean PCOS patients tended to have lower IGFBP-1 levels than

Figure 4 Relationships between calculated 12-h GH production rate and LH production rate (top) ($r = 0.65$, $P < 0.01$), as well as between the mass of GH and mass of LH secreted per burst (bottom) ($r = 0.74$, $P = 0.004$) in PCOS (●) and eumenorrheic controls (○). The solid line represents linear regression analysis of the PCOS data.

lean controls, the difference did not reach statistical significance (Table 3). The IGF-I/IGFBP-1 ratio was significantly higher in the PCOS (66.2 ± 15.5) than in the control group (27.1 ± 9.5), irrespective of BMI.

Insulin concentrations correlated negatively with IGFBP-1 for all patients and controls ($r = -0.53$, $P = 0.002$), and in the group of PCOS patients ($r = -0.60$, $P = 0.038$).

GH, LH and steroids

In the PCOS group, mean (12-h) serum GH concentrations were positively correlated with mean 12-h LH levels ($r = 0.75$, $P = 0.006$), the mass of LH secreted per burst ($r = 0.77$, $P = 0.002$), and the 12-h LH production rate ($r = 0.73$, $P = 0.005$; Fig. 3). These correlations were not found in the controls. PCOS patients also maintained a positive relationship between the 12-h GH production rate and the 12-h

LH production rate ($r = 0.65$, $P < 0.01$), as well as between the mass of LH and the mass of GH secreted per burst ($r = 0.74$, $P = 0.004$) (Fig. 4). These relationships were also present when only lean PCOS adolescents were considered.

Serum androstenedione concentrations in adolescents with PCOS were related to mean 12-h serum GH levels ($r = 0.60$, $P = 0.03$) and to the 12-h GH production rate ($r = 0.72$, $P = 0.02$) (Fig. 5). In contrast, serum concentrations of 17-OHP, testosterone, estradiol, estrone and SHBG were not related to any parameter of GH secretion in either group.

Discussion

To our knowledge, the present clinical study demonstrates for the first time that non-obese adolescents with PCOS exhibit an increase in pulsatile GH production rate and heightened orderliness of GH release patterns with normal serum concentrations of GHBP, IGF-I, IGFBP-1 and IGFBP-3. Moreover, GH secretion correlated positively with measures of LH production as well as with serum androstenedione concentrations in girls with PCOS but not in normal adolescents.

Previous studies offer only limited insights into the pulsatile characteristics of GH secretion in PCOS (1–4), which is due in part to an inadequate sensitivity frequency and/or duration of GH measurements. Other studies have not taken into account the strongly negative influence of obesity on GH release, or evaluated the several components of this system, such as GHBP, IGF-I and IGFBPs.

An early study using an adequate sampling frequency, appropriate controls and assays of several modulators of the GH–IGF-I axis (5) found a higher GH pulse amplitude in lean than in obese women with PCOS. In our study, the combined use of a highly specific and sensitive GH assay and deconvolution analysis allowed us to demonstrate that lean PCOS adolescents maintain greater mean (integrated) and pulsatile production of GH.

The fact that lean PCOS patients showed a significant increase in 12-h GH production rate and in the integrated GH concentration, without differences in the frequency of the pulses, suggested that the higher GH concentration found in this group of patients is an amplitude-modulated effect. In addition, this hypothesis is supported by the finding that patients with PCOS exhibited a tendency to secrete a higher mass of GH per burst than controls, without a difference in basal GH secretion. Clinical studies indicate that testosterone and estradiol both stimulate GH secretion via a common neuroendocrine mechanism of increased GH secretory burst amplitude or mass (24, 25). This steroidal effect is likely to be mediated by the estrogen receptor (26, 27). In healthy women, serum GH and IGF-I concentrations rise in the late

Figure 5 Correlations between 12-h serum GH concentrations (top) and GH production rates (bottom) with serum androstenedione concentration. In PCOS patients (●), calculated mean GH and GH production rates were positively related to androstenedione ($r = 0.60$, $P = 0.03$ and $r = 0.72$, $P = 0.02$ respectively). The continuous line represents the predicted regression for the PCOS data.

follicular phase of the normal menstrual cycle concomitantly with serum estradiol, yielding a positive relationship between GH and estradiol secretion. In men and boys, there is a positive correlation between serum testosterone concentrations and GH secretory burst mass and amplitude (28). Whereas estradiol levels were similar in PCOS and normal adolescents in the present study, testosterone and androstenedione concentrations were increased in patients with PCOS. In addition, serum androstenedione concentration correlated positively with GH production. An increment in androgen availability, and hence substrate for aromatization to estrogen, could modify both the quantity and the pattern of GH secretion.

Several mechanisms could mediate the present results. First, in principle, sex steroids could exert direct effects on GH secretion at the pituitary level. However, estradiol does not stimulate GH gene expression acutely either *in vivo* or *in vitro* (29, 30). Direct hypophyseal–portal blood sampling studies in several non-human species indicate that GH pulses mirror the hypothalamic discharge of GH-releasing hormone (GHRH) (31, 32), and that somatostatin (SRIH) restrains the actions of available GHRH (33). Thus, gonadal steroids may drive GH secretion by modulating hypothalamic GHRH/SRIH interactions (34–36). Estradiol and testosterone also regulate the orderliness of GH release (37). Indeed, in both the rodent and the human, the female maintains more irregular GH secretion (greater GH ApEn values) than the male (38). One proposed mechanism for this gender difference is a decrease in GH autofeedback inhibition of the somatotrophic axis in the female (39) and/or greater hypothalamic SRIH release in the male (31, 40). Accordingly, more orderly GH release (lower ApEn values) in adolescents with PCOS suggests that the more androgenic milieu in these patients may influence hypothalamic GHRH and SRIH signaling toward a more male-like pattern of GH release. In contradistinction, whereas estrogen administration also elevates GH burst mass and amplitude (41), it elicits more irregular GH secretory patterns (higher GH ApEn) in girls and women (37, 38).

Serum concentrations of GHBP were negatively related to the increase in night-time GH release in lean adolescents with PCOS, as indicated by higher integrated serum GH concentrations and augmented 12-h GH production rate. This inverse association is also evident in normal puberty (42). The physiological impact of a decline in GHBP concentrations on target tissues is not yet clear (43). In the present study, total serum IGF-I as well as IGFBP-3 concentrations were normal in PCOS patients. Nevertheless, normal serum concentrations of total IGF-I and IGFBP-3 do not exclude the possibility that free IGF-I levels are altered. Free IGF-I is controlled in part by IGFBP-1, which was reduced in the entire group of PCOS patients studied

here, albeit not in the lean subset. Thierry van Dessel *et al.* (44) reported higher free IGF-I concentrations in adults with PCOS and normal total IGF-I, IGF-II, and IGFBP-3. This distinction probably reflects the suppressive effect of hyperinsulinism on hepatic IGFBP-1 production (43). In this regard, the IGF-I/IGFBP-1 ratio was elevated in our PCOS cohort independently of the BMI. We speculate that increased free IGF-I availability, if confirmed in PCOS, could enhance androgen production by theca cells concurrently exposed to elevated LH drive, as inferred in *in vitro* studies (11, 45, 46). In addition, as suggested by Yen (47), GH may directly stimulate IGF production by granulosa cells, which target theca cells by paracrine effects on androgen biosynthesis.

LH pulsatility is often amplified in lean patients with PCOS (48–50). In the present study, lean PCOS adolescents maintained a strongly positive relationship between the 12-h outputs of GH and LH. The correlation between GH and LH pulse masses could indicate that a common neuroendocrine mechanism mediates the combined increase in LH and GH release. In addition to possible neurotransmitter mechanisms, reproductive hormones may regulate GH secretion by a subset of evidently plurisecretory gonadotrope cells, which are detectable in the (rat) pituitary gland (51).

In conclusion, the present clinical study shows that non-obese adolescents with PCOS secrete GH at a higher rate and with more orderly patterns, resembling a male profile. Determining whether this pattern reflects an intrinsic hypothalamic abnormality or is secondary to androgen excess in PCOS will require further studies.

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