Gonadotropin-Releasing Hormone Analog Plus an Oral Contraceptive Containing Desogestrel in Women With Severe Hirsutism: Effects on Hair, Bone, and Hormone Profile After 1-Year Use

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To evaluate the usefulness of D-Trp-6-luteinizing hormone–releasing hormone (LHRH) (triptorelin), a gonadotropin-releasing hormone (GnRH) analog (GnRHa), plus an oral contraceptive (OC) in the treatment of severe hirsutism, a total of 48 women between 19 and 35 years of age suffering from polycystic ovary syndrome (PCOS) with severe hirsutism were studied. Hyperandrogenism of adrenal origin was excluded in all subjects. Twenty-three patients received 3.75 mg D-Trp-6-LHRH intramuscularly monthly for 1 year plus an OC containing 30 μg ethinyl-estradiol and 150 μg desogestrel. A second group of 25 subjects received an OC containing 35 μg ethinyl-estradiol and 2 mg cyproterone acetate (CPA). Immediately before and after months 6 and 12 of therapy, bone mineral density (BMD) and Ferriman-Gallwey scores were evaluated and follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol (E2), prolactin (PRL), testosterone (T), androstenedione (A), dehydroepiandrosterone sulfate (DHEAS), 17-OH-progesterone (17-OHP), and sex hormone–binding globulin (SHBG) were determined. After 1 year of follow-up study, the combination of a GnRHa plus OC resulted in a decrease of hirsutism similar to that observed in the CPA group (41.9% *v* 40.5%) and in a suppression of gonadotropins and ovarian steroids in all treated women, without significant changes in bone density. The GnRHa-OC combination can potentially be used in the treatment of hirsutism and hyperandrogenism.

THE PRESENCE OF EXCESS hair growth in young women is not an uncommon problem. In most cases, it will depend on an increased production of androgens or on an increased sensitivity of the peripheral target organs.[1,2]

At present, the available choices for therapy are drugs that suppress the glandular production of androgens, eg, oral contraceptives (OCs)[3] and glucocorticoids,[4] and nonestrogenic antiandrogen drugs that act at a peripheral level.[5] However, the results of medical treatments have been poor or inconsistent, and although cosmetic measures may be useful, they will not change the underlying cause. Moreover, mechanical hair removal is not free of inconveniences such as intolerance, discomfort, and high cost. Because gonadotropin-releasing hormone (GnRH) analog (GnRHas) decrease or suppress ovarian steroid secretion, they have been suggested as potentially useful in the treatment of hirsutism.[6,7] However, since GnRHas suppress both androgen and estrogen levels, patients who receive these drugs alone may experience climacteric symptoms and decreases in bone mass. For this reason, estrogen-progestogen add-back therapy has been suggested. The aim of this study was to evaluate the applicability and safety of a combination of a long-acting GnRHa, triptorelin, plus an OC containing ethinyl-estradiol and desogestrel in the treatment of hirsutism.

SUBJECTS AND METHODS

Patients

After provision of informed consent, 48 women with polycystic ovary syndrome ([PCOS] oligomenorrhea/amenorrhea, high levels of ovarian androgens, hirsutism, and enlarged ovaries by ultrasonography) and complaining of severe hirsutism were allocated to two groups. The first (n = 23) was treated with an intramuscular injection of 3.75 mg triptorelin (Decapeptyl 3.75; Lasa-Ipsen, Barcelona, Spain) every 28 days for 12 consecutive months, starting after deprivation when they had menstrual cycles (oligomenorrheics) or during the first days of an induced cycle (oligomenorrheics/amenorrheics). These patients additionally received an OC containing 30 μg ethinyl-estradiol and 150 μg desogestrel (Microdiol; Organon, Sant Boi, Barcelona, Spain). The second group (n = 25) received an OC containing 35 μg ethinyl-estradiol and 2 mg cyproterone acetate (CPA) (Diane-35; Schering España, Madrid, Spain). Both OCs were administered for 12 consecutive cycles according to the standard 21 days on and 7 days off regimen. None of the subjects had been on any form of drug therapy for 6 months before taking part in the study. Oligomenorrheic/amenorrheic subjects received medroxyprogesterone acetate 5 mg/d for 10 days to induce a withdrawal bleeding before beginning the treatment. All subjects voluntarily entered this study, which was approved by the Ethics Committee of the Department.

Clinical data of the patients studied are summarized in Table 1. The age range of study subjects was 19 to 35 years. All had intact ovaries. Since basal levels of dehydroepiandrosterone sulfate (DHEAS) and 17-hydroxyprogesterone (17-OHP) were within the normal range in most cases, hyperandrogenism of adrenal origin was unlikely. In addition, during this study, in five cases in which 17-OHP was higher than 2 ng/mL, a corticotropin (ACTH) stimulation test was performed. Since ACTH-stimulated levels of 17-OHP were less than 6.0 ng/mL in all cases, we could rule out late-onset adrenal hyperplasia in such patients. Hypothyroidism and prolactinomas were excluded in all subjects. None of the patients smoked more than a half-pack per day. Hirsutism was evaluated according to a modification of the Ferriman-Gallwey scoring system,[8] in which a single observer (C.C.-B.) assessed hair growth in nine body areas (sideburns, upper lip, chin, chest, upper and lower abdomen, upper and lower back, and thighs) on a 0 to 4 scale. To reduce intraobserver variability, hirsutism scores from previous visits were blind for the attending physician.

The control group consisted of 20 eumenorrheic nonhirsute women presenting for contraception, aged 19 to 29 years (mean, 24.3 ± 3.2) with a mean body mass index of 22.5 ± 1.6. In these women, blood samples for hormone assays were taken in the early follicular phase. Subjects allocated to the control group received for 12 consecutive cycles the same OC as used in GnRH group.

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Table 1. Clinical Data

Parameter	Group	Basal	6 Months	12 Months
Hirsutism (FG)	A	24.6 ± 4.3*	17.2 ± 3.3*	14.3 ± 2.7*
	B	25.2 ± 1.3*	20.4 ± 5.1*‡	15.0 ± 2.2*
	C	<7	<7	<7
Body mass index	A	27.6 ± 2.0†	27.9 ± 4.5	27.0 ± 3.2†
	B	26.0 ± 2.7†	27.0 ± 3.5†	27.5 ± 6.2†
	C	22.5 ± 1.6	23.1 ± 2.7	23.1 ± 2.8
Systolic blood pressure (mm Hg)	A	127.6 ± 11.9	126.7 ± 17.1	127.1 ± 11.9
	B	126.2 ± 10.7	127.2 ± 14.1	128.7 ± 10.5
	C	122.6 ± 17.9	122.7 ± 18.3	122.9 ± 19.6
Diastolic blood pressure (mm Hg)	A	75.5 ± 7.7	74.0 ± 8.6	75.0 ± 5.8
	B	73.0 ± 8.9	72.0 ± 9.5	76.0 ± 3.1
	C	69.5 ± 12.6	71.0 ± 17.8	70.1 ± 17.3
BMD (g/cm²)	A	1.228 ± 0.28†	1.221 ± 0.27†	1.223 ± 0.21†
	B	1.231 ± 0.21†	1.232 ± 0.19†	1.230 ± 0.23†
	C	1.174 ± 0.18	1.173 ± 0.19	1.173 ± 0.17

NOTE. Values are the mean ± SD.

Abbreviations: FG, Ferriman-Gallwey score; A, GnRH-OC group (n = 23); B, CPA group (n = 25); C, nonhirsute group (n = 20).

*$P < .001$, †$P < .05$, PCOS *v* normal women.

‡$P < .05$, CPA *v* GnRH group.

Protocol

Before starting the treatment and after 6 and 12 months of therapy, all patients underwent a history and physical examination that included hirsutism evaluation, gynecological examination, pelvic ultrasound, bone mineral density (BMD) assessment in the lumbar spine, and hormonal assays that included follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol (E2), prolactin (PRL), testosterone (T), androstenedione (A), DHEAS, 17-OHP, and sex hormone–binding globulin (SHBG). Basal hormones were determined in the early follicular phase when subjects had regular menstrual cycles.

BMD Measurements

BMD in the lumbar spine was assessed by dual-energy x-ray absorptiometry (DEXA) (Lunar DPX system, Madison, WI) and expressed in grams per centimeter squared as the mean of the second to fourth lumbar vertebrae. DEXA uses stable k-edge radiation. The typical standard deviation for anterior-posterior lumbar spine in vivo is 0.01 g/cm². For a young normal individual with BMD of 1.2 g/cm², the coefficient of variation is 0.8%, and for an osteopenic patient (BMD < 0.8 g/cm²) 1.2%. The precision of the DPX system for spine is 0.5%, and patient exposure is low (1.2 to 2.4 mR for spine). All measurements were performed and analyzed by a single operator (F.P.).

Hormone Analysis

LH, FSH, E2, PRL, T, and A levels were measured before and at the end of each treatment period, using previously described methods.[7,9,10] DHEAS level was measured by coated-tube radioimmunoassay (Diagnostic Products, Los Angeles, CA). The antiserum is highly specific for DHEAS, with a relatively low cross-reactivity with other steroids: 17-β-E2 0.03%, E1 0.01%, E1-3-SO_4 0.5%, androsterone-SO_4 0.36%, T 0.10%, and A 0.12%. SHBG level was measured by a two-site fluoroimmunometric assay (Wallac, Turku, Finland). No human serum protein is known to cross-react with the polyclonal-monoclonal antibody combination used in this assay. The free testosterone index was calculated with the formula, T × 3.47/SHBG. The coefficients of variation have been previously described elsewhere.[11] Blood samples were taken in the morning between 8:30 and 10:00 AM, after an overnight fast and tobacco abstinence.

Statistical Analysis

Results are expressed as the mean ± SD. Statistical differences for paired data were determined by Student's *t* test and for unpaired data by Wilcoxon's test. Differences between means for repeated measures were determined by one-way ANOVA. *P* less than .05 was regarded as significant. Results were analyzed using the Statistical Analysis Package (Walonick, Minneapolis, MN).

RESULTS

Clinical Results

Baseline clinical data for women who participated in the study and data for the nonhirsute control group are shown in Table 1. No significant changes occurred in either body mass index or blood pressure during treatment.

Hair Growth

After 6 months of treatment with GnRH plus OCs, the total hirsutism score decreased by approximately 30.1% ($P < .001$) from 24.6 ± 3.1 (range, 16 to 32) to 17.2 ± 2.5 (range, 12 to 21), whereas decreases observed in CPA-treated patients were approximately 19% ($P < .01$) from 25.2 ± 3.2 (range, 17 to 31) to 20.4 ± 4.6 (range, 15 to 21). At 1-year follow-up evaluation, the Ferriman-Gallwey score decreased by 41.9% to 14.3 ± 3.7 (range, 9 to 18) ($P < .0025$) in the GnRH group, and by 40.5% to 15 ± 3.1 (range, 10 to 19) ($P < .0025$) in the CPA group. Although differences between the GnRH-OC group and CPA group were significant at 6 months ($P < .025$), at 1 year of follow-up study, both groups showed similar results in the decreasing hirsutism score (Figs 1 and 2). The upper lip (basal, 3.2; 12 months, 1.5), chin (basal, 3.0; 12 months, 1.2), and abdominal (basal, 2.9; 12 months, 1.2) hair proved to be the most responsive areas to GnRH-OC therapy.

Hormones

Hormone levels in the PCOS group and nonhirsute control group are listed in Table 2. As expected, patients with PCOS showed higher basal values for LH, T, A4, and 17-OHP and significantly lower values for SHBG than eumenorrheic subjects. After combined GnRHa-OC therapy, patients with PCOS

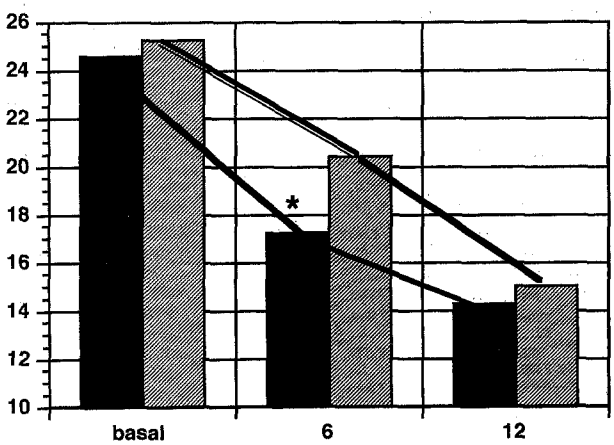

Fig 1. Ferriman-Gallwey scores after GnRH-OC therapy (■) and after OCs containing CPA (▨). Significant differences were detected at 6 but not at 12 months of therapy between both groups: *$P < .025$.

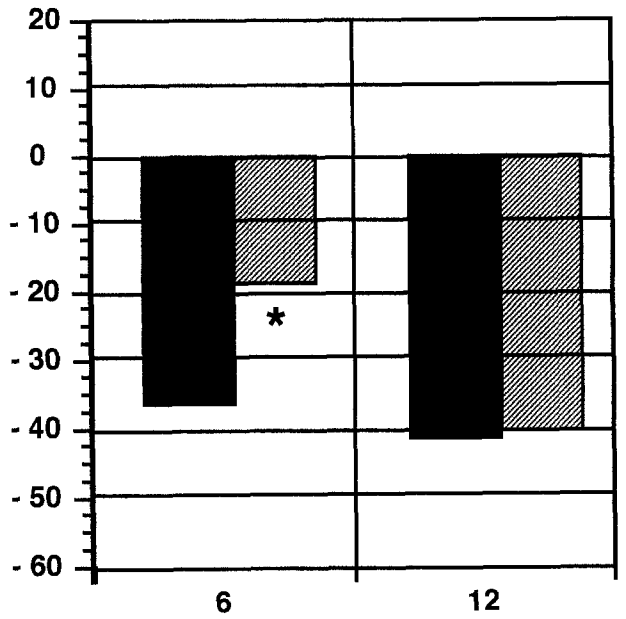

Fig 2. Differences in Ferriman-Gallwey scores after GnRH-OCs therapy (■) and after OCs containing CPA therapy (▨) expressed as percentage of change. Significant differences were detected at 6, but not at 12 months of therapy, between both groups. (*$P < .025$).

showed a significant reduction in LH (88% at 6 months [$P < .001$] and 90.7% at 12 months [$P < .001$]), FSH (96.5% at 6 months [$P < .001$] and 95.4% at 12 months [$P < .001$]), E2 (44.4% at 6 months [$P < .05$] and 55.5% at 12 months [$P < .05$]), T (81.6% at 6 months [$P < .01$] and 78.6% at 12 months [$P < .01$]), A (40.6% at 6 months [$P < .02$] and 43.1% at 12 months [$P < .02$]), and 17-OHP (54.5% at 6 months [$P < .02$] and 45.5% at 12 months [$P < .02$]). Patients with PCOS who received CPA showed similar changes in the hormonal profile after therapy (Table 2). Subjects in the nonhirsute control group treated with OCs showed less marked but still significant decreases in LH (81% at 6 months [$P < .01$] and 78% at 12 months [$P < .01$]), FSH (57% at 6 months [$P < .01$] and 60% at 12 months [$P < .01$]), E2 (38% at 6 and 12 months [$P < .05$], T (21.6% at 6 months [$P < .02$] and 16.5% at 12 months [$P < .02$]), A (18.9% at 6 months [$P < .05$] and 19.9% at 12 months [$P < .05$]), and OHP (3.3% at 6 and 12 months). After therapy, SHBG levels increased and the free T index was near 0% in both groups. PRL did not change during the study. And finally, although DHEAS was lower after treatment in all subjects, the changes were not significant.

Bone Density

BMD in lumbar spine (grams per square centimeter) of hirsute patients was in the upper-normal range (Table 1) and higher than the BMD observed in the normal control group ($P < .05$). No significant changes in bone mass were detected at 6 and 12 months of therapy in any of the groups.

DISCUSSION

Hirsutism is envisaged by the patient more as a psychosocial and cosmetic problem than a disease. In the therapeutic approach to hirsutism, emphasis has been placed on inhibition of the androgen-producing gland and blockade of androgen action at the pilosebaceous unit.[2] Different antiandrogenic drugs, such as flutamide,[12,13] CPA,[14] spironolactone,[12,15] and, more recently, finasteride,[16] constitute the resources in the basic approach to the treatment of hyperandrogenic manifestations. GnRHa effectively suppresses ovarian steroid production[17] and decreases ovarian steroid levels by suppressing pituitary LH and FSH secretion; for this reason, its use has been suggested as a new therapeutic approach in the treatment of hirsutism.[3,4,6,7,18] In the present study, the combined GnRHa-OC therapy has proven to be effective in reducing gonadotropins and ovarian steroid levels.

Our results demonstrate the applicability of the combination GnRHa-OC in the treatment of hirsutism. The use of such therapy resulted in a decrease of hirsutism scores at 6 months (30.1%) and 12 months (41.9%) as related to basal scores. Upper-lip, chin, and abdominal hair were the areas in which the effect of treatment was more apparent, as previously reported.[18]

Although GnRHa reduces ovarian steroid secretion to menopausal levels, there is no reason for estrogen suppression in the treatment of hirsutism, and addition of estrogen-progestogen replacement is adequate to avoid the deleterious effects of such a deficiency, eg, osteoporosis. Moreover, adding OCs to GnRHa

Table 2. Hormonal Data: Basal Levels and After 6 and 12 Months of Treatment in PCOS Patients With Hirsutism and the Nonhirsute Control Group

Parameter	Group	Basal	6 Months	12 Months
FSH (mIU/mL)	A	5.4 ± 1.9	0.6 ± 0.4*	0.5 ± 0.4*
	B	5.6 ± 1.2	0.9 ± 0.7*	0.4 ± 0.2*
	C	6.6 ± 1.4	1.2 ± 0.7†	1.4 ± 0.9†
LH (mIU/mL)	A	8.7 ± 2.4	0.3 ± 0.1*	0.4 ± 0.3*
	B	8.6 ± 4.4	0.2 ± 0.1*	0.4 ± 0.2*
	C	3.3 ± 1.1¶	1.4 ± 0.1†	1.3 ± 0.2†
PRL (ng/mL)	A	6.3 ± 2.6	5.1 ± 1.8	4.9 ± 2.3
	B	7.9 ± 4.3	8.1 ± 1.3	7.4 ± 2.3
	C	8.9 ± 3.3	7.1 ± 1.6	8.4 ± 2.7
E2 (pg/mL)	A	45.8 ± 17.9	25.0 ± 11§	20.8 ± 12.4§
	B	53.9 ± 21.4	25.8 ± 12§	22.9 ± 11.4§
	C	43.9 ± 12.4	26.8 ± 19§	26.9 ± 17.4§
T (ng/dL)	A	98.6 ± 19.7	18.7 ± 12.7†	21.6 ± 9.4†
	B	111 ± 29.2	19.7 ± 11.7†	19.3 ± 9.7†
	C	31.5 ± 09.4¶	24.7 ± 9.7‡	26.3 ± 7.7‡
A4 (ng/dL)	A	261.9 ± 47.7	151.1 ± 26.7‡	149.4 ± 31‡
	B	289.4 ± 31.7	154.7 ± 33.2‡	151.7 ± 28.2‡
	C	199.4 ± 31.0#	164.2 ± 21.9§	159.7 ± 22.4§
DHEAS (mg/mL)	A	2.4 ± 0.9	2.1 ± 0.4	2.0 ± 1.2
	B	2.7 ± 1.3	2.3 ± 0.7	1.9 ± 1.4
	C	2.1 ± 1.1	2.1 ± 0.2	1.9 ± 0.9
17-OHP (ng/mL)	A	1.1 ± 0.5	0.5 ± 0.2‡	0.6 ± 0.3‡
	B	1.2 ± 0.8	0.4 ± 0.3‡	0.5 ± 0.3‡
	C	0.6 ± 0.3#	0.4 ± 0.2	0.4 ± 0.1
SHBG (nmol/L)	A	25.7 ± 26.8	148.5 ± 39.1*	167.8 ± 45.1*
	B	24.5 ± 18.3	185.8 ± 45.4*	186.9 ± 45.7*
	C	54.5 ± 08.2¶	158.8 ± 25.6*	166.9 ± 37.7*
Free index	A	12.6 ± 3.17	0.43 ± 0.11*	0.44 ± 0.12*
	B	14.9 ± 3.17	0.33 ± 0.16*	0.34 ± 0.21*
	C	2.00 ± 0.85‖	0.41 ± 0.21*	0.42 ± 0.22*

Values are the mean ± SD.

*$P < .001$, †$P < .01$, ‡$P < .025$, §$P < .05$: *v* basal.

‖$P < .001$, ¶$P < .01$, #$P < .05$: control group *v* PCOS.

therapy may improve the clinical results, since the progestin will decrease ovarian androgen and estrogen production not only by inhibiting gonadotropin secretion but also by binding to the glucocorticoid receptor, and this may result in a reduction of adrenal androgen secretion.[3] However, in the present study, the observed reduction in DHEAS levels was mild and nonsignificant. Furthermore, the estrogen component of OCs increases SHBG, producing a sharp decrease of free T. Since the main goal was to evaluate the usefulness of a GnRHa-OC combination in the treatment of hirsutism and the present study has a nonhirsute normal control group, we selected an OC with a progestin (desogestrel) having negligible androgenic/antiandrogenic activity.[3] Clearly an OC containing a progestin with antiandrogenic properties such as CPA would have been more attractive for such patients, but its use in the present study would have been confusing for the interpretation of how GnRH therapy affects hirsutism. Moreover, although at 1 year of follow-up study the observed decrease in the Ferriman-Gallwey score was similar for both PCOS groups, the combined GnRH-OC therapy resulted in a larger decrease of Ferriman-Gallwey scores at 6 months compared with CPA. This fact may have several clinical implications. First, one must keep in mind that severe hirsutism in young patients usually is accompanied by psychological problems, and a faster improvement of hirsutism might improve the psychosocial component. And second, these initial results suggest a new therapeutic approach to hirsutism, starting the treatment with a combined therapy of GnRH plus OC for 6 months to obtain the maximum effect in reducing hair growth, and thereafter continuing with a pure antiandrogen as standard therapy.

Moreover, triptorelin-ethinyl estradiol-desogestrel combined therapy did not induce any remarkable side effects or changes in bone mass after 1 year of use. Standard postmenopausal estrogen replacement therapy has been shown to be ineffective in preventing vertebral bone loss in premenopausal women under GnRHa suppression[19]; however, no bone loss was observed in any subject of this study after 6 or 12 months of maintained GnRHa-OCs administration. Although these results support data from previous reports[18,20,21] that failed to find a decrease in BMD after add-back OCs as estrogen-progestin replacement to GnRHa therapy, the data are limited to 12 months and further studies are needed to address this issue.

Finally, although a transiently greater improvement at 6 months could be obtained with the GnRHa-OCs combined therapy, one must recognize that this advantage may only be justified in subjects who complaint of severe hirsutism and that, in other cases, the additional cost and inconvenience of analog do not justify its use.

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