The Efficacy and Safety of Gonadotropin-Releasing Hormone Analog Treatment in Childhood and Adolescence: A Single Center, Long-Term Follow-Up Study

Maria Alexandra Magiakou,* Despoina Manousaki,* Marina Papadaki, Dimitrios Hadjidakis, Georgia Levidou, Marina Vakaki, Athanassios Papaefstathiou, Niki Lalioti, Christina Kanaka-Gantenbein, George Piaditis, George P. Chrousos, and Catherine Dacou-Voutetakis

Division of Endocrinology, Metabolism, and Diabetes (M.A.M., D.M., N.L., C.K.-G., G.P.C., C.D.-V.), First Department of Pediatrics, Athens University Medical School, Aghia Sophia Children's Hospital, and Department of Pathology (G.L.), Athens University Medical School, and Department of Radiology (M.P., M.V.), P. and A. Kyriakou Children's Hospital, and Department of Endocrinology and Diabetes Center (G.P.), General Hospital of Athens, 11527 Athens, Greece; and Endocrine Unit (D.H., A.P.), 2nd Department of Internal Medicine-Propaedeutic, Athens University Medical School, Attikon University Hospital, 12462 Athens, Greece

Objective: The objective of the study was to evaluate the long-term effect of GnRH analog (GnRHa) treatment on final height (FH), body mass index (BMI), body composition, bone mineral density (BMD), and ovarian function.

Subjects/Methods: Ninety-two females, evaluated in adulthood, were categorized as follows: group A, 47 girls with idiopathic central precocious puberty (33 GnRHa treated and 14 nontreated); group B, 24 girls with isolated GH deficiency (15 GnRHa and GH treated and nine GH treated); group C, 21 girls with idiopathic short stature (seven GnRHa and GH treated, seven GnRHa treated, and seven nontreated).

Results: FH, BMD, and percent fat mass of GnRHa-treated patients in all three groups were comparable with those of the respective nontreated subjects. BMI values of GnRHa-treated and nontreated subjects in groups A and C were comparable, whereas in group B, a higher BMI was found in subjects treated only with GH. Nontreated patients with ICPP had greater maximal ovarian volumes, higher LH and LH to FSH ratio, and more severe hirsutism than GnRHa-treated ones. Menstrual cycle characteristics were not different between treated and nontreated subjects. The prevalence of polycystic ovary syndrome in treated and untreated girls with ICPP was comparable, whereas in the entire cohort, it was 11.1% in GnRHa treated and 32.1% in the untreated ($P = 0.02$).

Conclusions: Girls treated in childhood with GnRHa have normal BMI, BMD, body composition, and ovarian function in early adulthood. FH is not increased in girls with ICPP in whom GnRHa was initiated at about 8 yr. There is no evidence that GnRHa treatment predisposes to polycystic ovary syndrome or menstrual irregularities. **(*J Clin Endocrinol Metab* 95: 109–117, 2010)**

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* M.A.M. and D.M. contributed equally to this work.

Abbreviations: BA, Bone age; BMD, bone mineral density; BMI, body mass index; CA, chronological age; CPP, central precocious puberty; DHEAS, dehydroepiandrosterone sulfate; DXA, dual-energy x-ray absorptiometry; FH, final height; FFM, fat-free mass; FM, fat mass; GnRHa, GnRH analog; GP, Greulich and Pyle; HOMA, homeostasis model assessment; ICPP, idiopathic central precocious puberty; ISS, idiopathic short stature; LM, lean mass; MC, menstrual cycle; PAH, predicted adult height; PAHacc, predicted adult height using accelerated standards of GP; PAHav, predicted adult height using average standards of GP; PCOS, polycystic ovary syndrome; SDS, SD score; WHR, waist to hip ratio.

For almost 30 yr GnRH analogs (GnRHas) have been used in the management of central precocious puberty (CPP). GnRHas have also been used to increase the final height (FH) of children with early puberty, and patients with GH deficiency (GHD) or idiopathic short stature (ISS) and normally timed puberty, who have short stature at puberty onset (1–6). Whether FH improves with GnRHa treatment has not been definitively answered yet (1–11), whereas the long-term consequences of GnRHa treatment on body mass index (BMI) (9–13), bone mineral density (BMD) (9–11, 14–18), body composition (10–12, 15, 17), and reproductive function (9–11, 19, 20) are still under scrutiny.

In this single-center study, 92 young women, aged 16–32.3 yr, seen with the initial diagnosis of idiopathic CPP, isolated GHD, and ISS, had their FH, BMI, BMD, body composition, and ovarian function evaluated in late adolescence and early adulthood. Each of the three groups included patients who received or did not receive GnRHa treatment.

Subjects and Methods

Subjects

The study included girls with idiopathic CPP (ICPP), idiopathic GHD or ISS followed up in our Endocrine Unit from 1986 to 2005 and either received (treated) or did not receive (untreated) GnRHa treatment. In the latter group, treatment was suggested but the parents refused. We called all patients, who had reached late adolescence and adulthood (n = 208), informed them about the present study, and invited them to come for reevaluation. Of the 208 invited patients, a total of 92 agreed to participate: 62 treated with GnRHa (representing 73.8% of the invited) and 30 untreated (representing 24% of the invited). In the nontreated patients, who were finally included, various parameters [chronological age (CA), bone age (BA), height SD score (SDS) for CA and BA, predicted adult height (PAH), BMI SDS, pubertal stage, LH and FSH basal and peak values, LH to FSH ratio, ovarian volume] did not differ from the respective whole cohort of untreated patients. The study was approved by the Scientific and Ethics Committee of the Aghia Sophia Children's Hospital, and all participants provided written informed consent before entry.

The patients were categorized into three main groups.

Group A

Forty-seven girls with ICPP, of whom 33 received GnRHa treatment (subgroup A1), and 14 received no treatment (subgroup A2). GnRHa depot (triptorelin, Arvekap, Ipsen Pharma Biotech, Paris, France) was given im every 25–30 d for a median period of 2.75 yr (range 1–5.16 yr) at a dose ranging from 2.86 to 6.98 μg/kg · d, which led to suppression of the hypothalamic-pituitary-gonadal axis throughout the duration of treatment, as reflected in the gonadotropin values during GnRH testing.

Group B

Twenty-four girls with isolated idiopathic GHD, of whom 15 received GH and GnRHa treatment (subgroup B1) and nine received only GH treatment (subgroup B2). GnRHa was given im every 25–30 d for a median period of 2.33 yr (range 0.83–2.83 yr) at a dose ranging from 3.06 to 5.36 μg/kg · d.

Group C

Twenty-one girls with ISS, of whom seven received no treatment (subgroup C1), seven received GH and GnRHa (subgroup C2), and seven received only GnRHa (subgroup C3). GnRHa was given im every 25–30 d for a median period of 3.17 (subgroup C2) and 2.67 yr (subgroup C3) and at a dose ranging from 3.57 to 6.52 and 3.6 to 5.77 μg/kg · d, respectively.

GH was administered sc by daily injections at a dose of 0.5 IU/kg · wk at bed time.

Methods

Initial evaluation and follow-up

All patients were evaluated as outpatients every 6 months throughout the follow-up period at the First Department of Pediatrics, Athens University Medical School. Height, weight, pubertal stage, and BA were precisely determined in all patients. BMI was calculated using the formula: weight (kilograms)/height (meters)^2. Pubertal staging was based on Tanner's criteria (21). Bone maturation was evaluated by a radiograph of the left hand and wrist, at least once a year, using the standards of Greulich and Pyle (GP) (22), and read centrally and blindly by an experienced investigator. Target height was calculated using the formula: mother + father height − 13/2 (23). The Bayley-Pinneau tables were used for the determination of PAH, and for patients of group A, the estimation was made by using both average and accelerated standards (24).

All girls of group A fulfilled the clinical and hormonal criteria of ICPP (breast development before the age of 8 yr, LH response to GnRH stimulation test >7 mIU/ml). Brain magnetic resonance imaging and a GnRH test were carried out in all subjects at initial evaluation. LH and FSH were determined before and 30 and 60 min after the iv administration of 100 μg of native GnRH. In all girls treated with GnRHa, the GnRH test was also performed at different intervals during GnRHa therapy and 6–12 months after its discontinuation. A pelvic ultrasound was available in 28 of 47 patients at initial evaluation.

All girls with short stature underwent a GH stimulation test at initial evaluation (glucagon, clonidine, or L-dopamine). The diagnosis of GHD was made if maximal GH values were less than 10 ng/ml in two GH stimulation tests. Multiple pituitary hormone deficiencies, organic abnormalities in the hypothalamic-pituitary region, and other causes of short stature (chronic illness, celiac disease, dysmorphic syndromes, *etc.*) had been excluded. ISS was diagnosed if the height SDS was less than −2 and GH values during a GH stimulation test were greater than 10 ng/ml.

Final evaluation

Final evaluation was carried out in all 92 subjects at a median age of 17.98 yr (range 16–32.3). They all had reached FH and had stopped any treatment (GnRHa or GH) at least 1 yr earlier.

An interim history was obtained. The characteristics of menstrual cycles (MCs; secondary amenorrhea, oligomenorrhea,

regularity, dysmenorrhea) and history of pregnancy and its outcome were recorded using a semistructured interview carried out by an expert clinician. Height, weight, waist and hip circumference, and signs of hyperandrogenism (acne, hirsutism) were recorded. Hirsutism was assessed using the Ferriman and Gallwey scale (25). Waist to hip ratio (WHR) was assessed according to Fredriks *et al.* (26).

A blood sample was obtained after an overnight fasting on d 3–6 of the MC for determination of basal levels of glucose, insulin, free T4, TSH, prolactin, LH, FSH, estradiol, 17-hydroxyprogesterone, SHBG, testosterone, and dehydroepiandrosterone sulfate (DHEAS). A repeat blood sample was obtained on the 21st day of the MC for determination of progesterone. Insulin, TSH, prolactin, LH, FSH and testosterone values were determined using the automated chemiluminescence system ACS:180 (Siemens Medical Solutions Diagnostics, Europe Ltd., Dublin, Ireland). SHBG and 17-hydroxyprogesterone were measured by double-antibody RIA (Immunotech, Prague, Czech Republic) and estradiol and progesterone by chemiluminescent microparticle immunoassay-CMIA (Architect system; Abbott Diagnostics, Indianapolis, IN). DHEAS was determined using the IMMULITE 2000 analyzer (Siemens Medical Solutions Diagnostics Limited, Gwynedd, UK).

Homeostasis model assessment (HOMA) index was calculated as fasting insulin concentration (microunits per milliliter) × fasting glucose concentration (millimoles per liter)/22.5, assuming that normal young subjects have an insulin resistance of 1. The present HOMA cutoff point for diagnosis of insulin resistance is 3.1 (27).

Transabdominal pelvic ultrasonography was performed by the same sonographer, using a LOGIC 7 apparatus with a 3,5–5 convex transducer (GE, Indianapolis, IN), during the first half of the MC. Uterine and ovarian size and structure were extensively evaluated. Ovarian structure and volume were assessed using the normative data reported by Salardi *et al.* (28) and the sonographic polycystic ovary syndrome (PCOS) characteristics were determined based on the guidelines of the Rotterdam consensus of 2003 (29).

BMD was measured in the total body at the lumbar spine (L1-L4) and the upper femur (two regions: total hip and femoral neck) by dual-energy x-ray absorptiometry (DXA) using a Hologic QDR series, Discovery-W densitometer of fan beam technology (Hologic, Bedford, MA). The precision *in vitro* using an appropriate spine phantom of the manufacturer was 0.36%, whereas the *in vivo* precision in our laboratory obtained by repeated measurements after repositioning of the same patient was 1% for lumbar spine (33 persons measured) and 1.1% for total hip (15 patients measured). BMD is expressed in grams per square centimeter and sex and age-adjusted values (Z scores) (30, 31).

Whole-body composition was measured by DXA scans performed on the aforementioned densitometer. Fan-beam technology was applied. Total mass, percent body fat, fat mass (FM), and fat-free mass (FFM) were measured for all individuals. All DXA scans were analyzed by the same person in a semiautomatic fashion including manual modifications of the regions of interest. Body composition data were presented as FM in grams, lean mass (LM) in grams, and bone mineral content in grams. FFM from DXA was calculated as LM + bone mineral content. Data were calculated separately for the different body subregions (left arm, right arm, trunk, pelvis, left leg, and right leg) as well as subtotal (excluding the head) and total values. Precision was determined from duplicate measurements of 11 female subjects with a mean BMI value of 31.1 kg/m^2. They were randomly selected from the female study participants. All retests were performed on the same day within a very short time period. The *in vivo* coefficient of variation was 1.53% for fat %, 1.86% for FM, and 0.87% for FFM, respectively.

Statistical analysis

Greek longitudinal normative data were used as standards for the calculation of height, weight, and BMI SDSs (32, 33). Data are presented as median and range. Due to the small sample size in each stratum, we did not assume normality of the distribution of the data, and comparisons were performed using nonparametric tests, such as Kruskal Wallis ANOVA and Mann Whitney *U* test, as appropriate. In each case that a statistical difference was elicited in the Kruskal-Wallis ANOVA test, we performed a *post hoc* analysis using Bonferroni correction for multiple comparisons. Fisher's exact test was used to calculate possible differences between percentages. Logistic regression analysis was used to adjust the differences in PCOS prevalence and BMD values among various groups for significant parameters. Statistical calculations were performed using the Statistical package STATA 9.0/SE for Windows (Stata Corp., College Station, TX). All results with a two-sided $P \leq 0.05$ were considered statistically significant.

Results

Initial evaluation and follow-up

Group A

Clinical and hormonal data of GnRHa-treated (subgroup A1) and nontreated subjects (subgroup A2) are depicted in Table 1. Significant differences between the two subgroups were detected only in pubic hair staging, basal LH values, and basal LH to FSH ratios.

Group B

The two subgroups (B1 and B2) were not different in terms of median BA (11 *vs.* 10.5 yr), height SDS for CA (−2.4 *vs.* −2.76) and BA (−1.9 *vs.* −1.25), PAH (152.5 *vs.* 154 cm), BMI SDS (0.02 *vs.* 0.115), pubertal stage, and peak GH values in the stimulation tests (7.7 *vs.* 6.3 ng/ml). The duration of GH treatment was longer in patients of subgroup B1 (4.6 *vs.* 2.5 yr, $P < 0.01$).

Group C

The three subgroups (C1, C2, and C3) were not different in terms of median CA (11 *vs.* 10.8 *vs.* 11.2 yr), BA (9.2 *vs.* 10 *vs.* 10.7 yr), height SDS for CA (−1.89 *vs.* −2.57 *vs.* −1.72), BMI SDS (−0.85 *vs.* −0.02 *vs.* −0.5), pubertal stage, and peak GH on provocative testing (15.1 *vs.* 14.6 *vs.* 20.6 ng/ml). PAH was lower in patients who received combined GnRHa and GH treatment (148.4 cm), compared with the nontreated ones (154.9 cm) ($P < 0.03$).

TABLE 1. Clinical parameters and hormonal profile of treated and nontreated girls with ICPP (group A) at start of treatment (A1) and at initial evaluation of the nontreated (A2)

	GnRHa treated (n = 33, A1)			Nontreated (n = 14, A2)			
	Median	Range	n	Median	Range	n	*P* value
CA (yr)	7.92	6.42–10.75	33	7.955	6.83–10	14	0.7979
Referred age at start of puberty (yr)	6.75	5–8.17	15	6.625	5.42–8	6	0.8865
BA (yr)	10	8.5–12	28	10.75	7.83–12.85	12	0.1721
Height SDS for CA	0.66	−1.78 to 3.05	33	1.22	−3.49 to 3.51	14	0.2392
Height SDS for BA	−1.68	−3.46 to 0.29	28	−1.435	−2.83 to 1.57	12	0.2496
BMI SDS	0.235	−1.15 to 7.42	33	0.375	−1.21 to 2.51	14	0.7624
PAHav (cm)	151.53	140.27–162.95	28	154.265	144.73–169.43	12	0.0741
PAHacc (cm)	158.16	144.8–169.72	28	160.28	147.4–176.76	12	0.1526
Breast stage	3	2–4.5	33	3.25	2–4.5	14	0.3641
Pubic hair stage	2	1–3	33	3	1–5	14	0.0123[a]
LH basal (mIU/ml)	1	0.1–6.7	33	2.1	0.3–12.6	14	0.0423[a]
FSH basal (mIU/ml)	3.8	0.1–13.5	33	3.15	1–14.6	14	0.7958
LH peak (mIU/ml)	14.4	7–49	33	7.6	7–80	14	0.4223
FSH peak (mIU/ml)	13.1	3.5–40.9	33	10.1	6.3–39.1	14	0.4807
LH to FSH ratio basal	0.19	0.05–20	33	0.985	0.11–4.36	14	0.0144[a]
LH to FSH ratio stimulated	1.1	0.15–4.54	33	1.09	0.33–5.36	14	0.3740
Ovarian volume (ml)	2.15	0.73–10.6	22	2.6	1–4.1	6	0.9554

[a] All results with a two-sided $P \leq 0.05$ are considered statistically significant.

Long-term results

Analysis within Groups

Group A. Final evaluation data of these patients are depicted in Table 2 and their auxological outcome in Fig. 1. The age at menarche was greater in the treated subjects ($P = 0.0001$). The FH was comparable in the two subgroups, and the ΔFH-PAH did not differ using either average or accelerated standards of GP for PAH calculation. When PAH was calculated using the average standards of GP, the median ΔFH-PAH using average standards of GP (PAHav) was 6.96 and 3.34 cm, whereas when the accelerated standards were used, the median ΔFH-PAH using accelerated standards of GP (PAHacc) was 1.7 and −1.2 cm in GnRHa-treated and nontreated subjects, respectively (P = ns). ΔFH-PAHav and Δ FH-PAHacc were comparable among the nontreated subjects ($P = 0.21$); however, ΔFH-PAHav was significantly higher than ΔFH-PAHacc among GnRHa-treated subjects ($P = 0.01$) as well as the whole ICPP group ($P = 0.006$). The nontreated patients had greater maximal ovarian volume ($P = 0.02$), higher LH to FSH ratio ($P = 0.04$), and higher Ferriman-Gallwey score ($P = 0.02$) than the GnRHa-treated subgroup. The PCOS prevalence in the GnRHa-treated subgroup (17.2%) was lower than in the nontreated subgroup (30.8%), but the difference was not significant ($P = 0.323$).

Group B. The GH-treated patients had higher BMI ($P = 0.01$) and BMI SDS ($P = 0.01$) than patients treated with GnRHa and GH. All the other parameters did not differ between the two subgroups. The auxological data are depicted in Fig. 2.

Group C. The median age at reevaluation of GnRHa-treated and untreated patients with ISS was 17 and 23.3 yr, respectively ($P = 0.03$). The median age at menarche of GnRHa and GH-treated and nontreated girls with ISS was 15.08 and 13.83 yr, respectively ($P = 0.01$). All the other parameters did not differ among the three subgroups. The auxological outcome is depicted in Fig. 3.

Glucose and HOMA values and hormonal profiles between patients of all subgroups did not differ significantly.

Analysis in the total group: GnRHa-treated vs. nontreated patients

The data at final evaluation of these two groups, irrespective of other treatment modalities, are depicted in Table 3.

BMI, BMD, and body composition were comparable in the two groups, and no differences in the duration of MC, days of bleeding, dysmenorrhea, use of contraceptives, and number of normal pregnancies and abortions were found. The median age at menarche in the nontreated group was lower (11.8) than that in the GnRHa-treated group (13 yr), as expected ($P = 0.009$).

Signs of clinical hyperandrogenism (acne, hirsutism), serum testosterone, Δ_4-androstendione, and DHEAS values, and sonographic ovarian findings (maximal ovarian volume and percentage of patients with follicles > 12) did not differ between GnRHa-treated and nontreated patients. However, the percentage of patients with ovarian volume greater than 10 ml, the basal LH values, and the LH to FSH ratios were higher in nontreated patients compared with the GnRHa treated ($P = 0.03$, $P = 0.01$, and $P = 0.0008$, respectively). Based on the National Institutes

TABLE 2. Data at final evaluation of patients with ICPP

Characteristics	GnRHa treated (n = 33, A1)			Nontreated (n = 14, A2)			*P* value
	Median	Range	n	Median	Range	n	
Age at reevaluation (yr)	17.5	16–28.67	33	18.96	16–32.33	14	0.0888
Auxological outcome							
FH (cm)	158.5	145–168.5	33	161.5	142.5–170	14	0.2782
ΔFH-TH (cm)	−0.25	−11.1 to 13	30	0.3	−12 to 8.5	12	0.7854
ΔFH-PAHav (cm)	6.955	−3.04 to 15.84	26	3.339	−2.83 to 15.59	12	0.3030
ΔFH-PAHacc (cm)	−1.7	−10.06 to 11.91	26	−1.19	−6.76 to 10.38	12	0.270
Obesity							
BMI (kg/m^2)	24.335	19.02–41.11	33	23.2	19.5–52.7	14	>0.999
BMI SDS	0.535	−0.89 to 4.45	33	0.37	−0.76 to 7.23	14	0.8119
WHR	0.83	0.7–0.92	33	0.83	0.7–1.01	14	0.4870
Bone density							
BMD (L1–L4, g/cm^2)	1.045	0.846–1.371	23	1.078	0.808–1.489	11	0.713[a]
Z score	−0.35	−1.5 to 3.2	18	0.45	−1.9 to 2.38	10	0.2909
Body composition							
FM (%)	35.4	30.8–48.7	15	33.4	22.4–46.7	7	0.4174
LM (%)	61.28	48.08–65.28	15	62.86	50.93–54.23	7	0.3413
Ovarian function							
Age at menarche (yr)	12	8.58–13.58	33	9.58	7–12	14	0.0001[b]
MC (d)	29	20–40	30	30	27–35	13	0.6456
Days of bleeding	5.5	4–10	30	5	3–6	13	0.0692
Clinical hyperandrogenism							
Acne (%)		33.34 (10/30)			30.77 (4/13)		0.413
Ferriman-Gallwey score	6	4–12	30	9	4–18	13	0.0195[b]
Indices of PCOS							
Ovarian volume (ml)	6.98	3.75–11.6	26	8.74	4.99–18.8	13	0.0193[b]
Ovarian volume greater than 10 ml (%)		0 (0/26)	26		23.07 (3/13)	13	0.0219[b]
Number of follicles 12 or greater (%)		7.7 (2/26)	26		30.7 (4/13)	13	0.1004
LH to FSH ratio	0.68	0.21–3.02	30	1.25	0.29–1.79	13	0.0467[b]
LH (mIU/ml)	3.425	0.7–20.7	30	4.3	1.4–9.83	13	0.3337
FSH (mIU/ml)	4.95	2.0–7.4	30	4.4	1.9–8.0	13	0.1925
PCOS prevalence (%)		17.24 (5/29)			30.77 (4/13)		0.3233

TH, Target height.

[a] The result is height-adjusted.

[b] All results with a two-sided $P \leq 0.05$ are considered statistically significant.

of Health criteria (clinical or biochemical hyperandrogenism and chronic anovulatory cycles) 32.1% (nine of 28) of nontreated and 11.1% (six of 54) of GnRHa-treated patients had PCOS ($P = 0.019$). After adjusting the PCOS prevalence for BMI SDS at diagnosis, age at evaluation, and time since menarche, a trend for higher values persisted for the first two factors ($P = 0.035$ and $P = 0.04$, respectively), but it was lost for the third ($P = 0.078$).

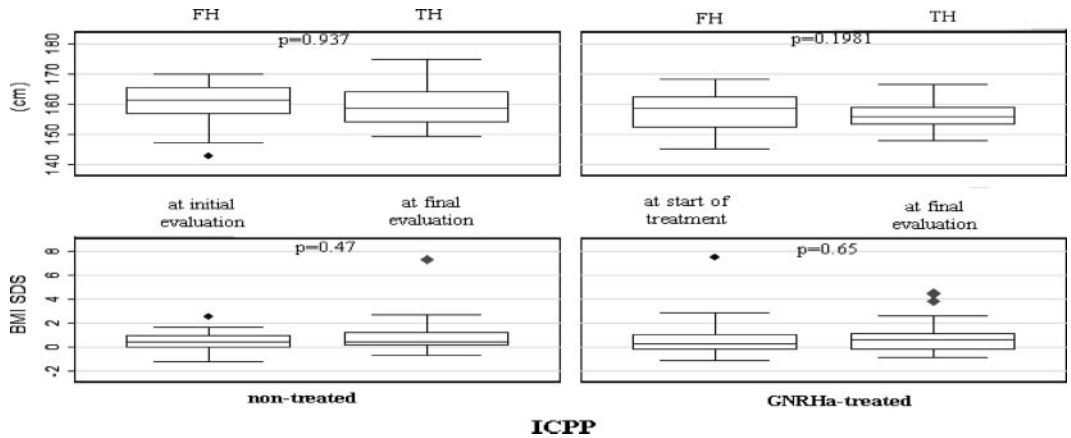

FIG. 1. Auxological outcome of patients with ICPP. The *line inside the boxes* represents the median value, the *lower border of the box* the 25th percentile, and the *upper border* the 75th percentile of the observations. *Spots* define outliers. TH, Target height; $P \leq 0.05$ is considered statistically significant.

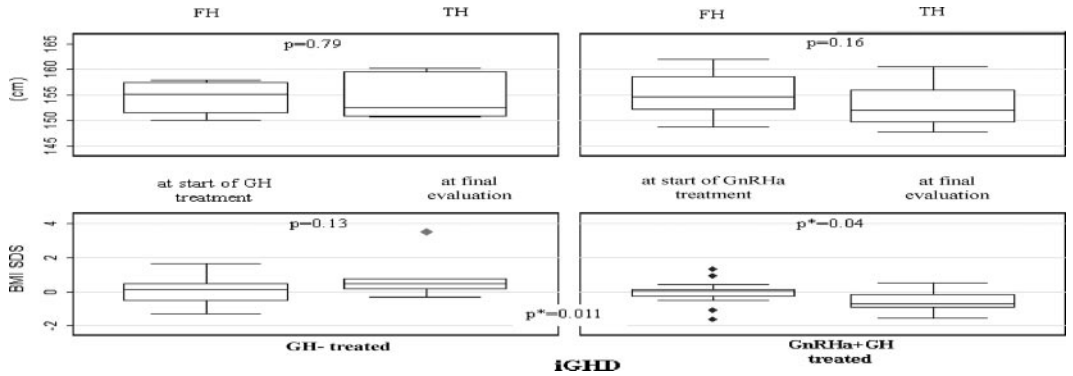

FIG. 2. Auxological outcome of patients with iGHD. The *line inside the boxes* represents the median value, the lower border of the box the 25th percentile, and the *upper border* the 75th percentile of the observations. *Spots* define outliers. iGHD, Isolated GHD. *, $P = 0.011$, BMI SDS at FH comparison between GH treated and GnRHa + GH treated. $P \leq 0.05$ is considered statistically significant.

Discussion

In this study we investigated the efficacy and long-term safety of depot GnRHa treatment in three groups of patients representing the main clinical entities [early puberty, isolated GHD, ISS] in which GnRHa treatment has been used for FH improvement. Patients matched for certain characteristics who refused GnRHa treatment are designated as nontreated control group.

Despite many studies, the question whether FH improves with GnRHa treatment has not received a definitive answer (1–11). The question of GnRHa treatment for FH improvement in early puberty (pubertal onset around 8 yr of age) (3, 4, 7, 8), and pubertal patients with either GHD (5) or ISS (6) are inconclusive. Our results indicate that no essential improvement in FH is achieved by the use of GnRHa in the entities studied because the FH of treated and nontreated subjects was comparable. The variety in reported results may be related to differences in the use of end points, lack of inclusion of proper control groups, and variability of individual responses. With regard to the ICPP group, the FH of our GnRHa-treated girls, presented at a median age of 7.92 yr, did not differ from the FH achieved by those without therapy, whereas their PAH was comparable. In a recent study by Pasquino *et al.* (11), in which 87 GnRHa-treated (age 6.5 yr) and 32 nontreated girls with ICPP (age 6.8 yr) were analyzed, the FH of treated and nontreated girls was 159.8 and 154.4 cm, respectively ($P < 0.01$). The girls included in that study were younger than ours, and triptorelin was given for a longer period, possibly explaining the favorable results on FH. Hence, in treating girls with puberty initiation at about 8 yr of age, the improvement in FH is minimal, if any.

A critical issue in assessing effectiveness of GnRHa treatment is the end point used. To this direction the difference between PAH and FH achieved has frequently been used as a criterion of effectiveness. As is shown by our analysis in the ICPP group using the ΔFH-PAH as an end point of effectiveness, the results are different, depending on the GP standards used for PAH calculation (average *vs.* accelerated); using the average standards the PAH is underestimated (151.5 *vs.* 158.5 cm of FH achieved), indi-

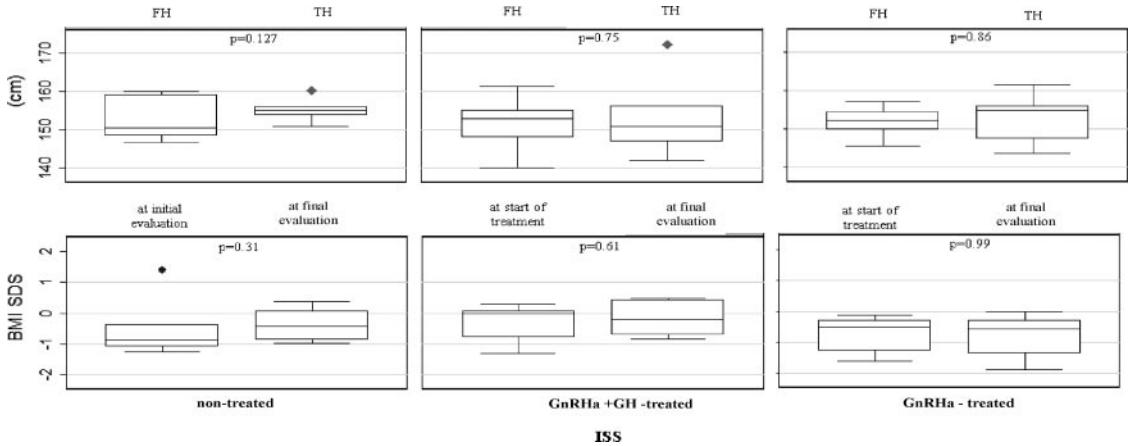

FIG. 3. Auxological outcome of patients with ISS. The *line inside the boxes* represents the median value, the *lower border of the box* the 25th percentile, and the *upper border* the 75th percentile of the observations. *Spots* define outliers. TH, Target height. $P \leq 0.05$ is considered statistically significant.

TABLE 3. Data at final evaluation of all patients (treated with GnRHa and nontreated)

Characteristics	Nontreated (30 patients) Median (range), n	GnRHa treated (62 patients) Median (range), n	*P* value
Age at reevaluation (yr)	19.92 (16–32.33), 30	17.46 (16–28.67), 62	0.0333[a]
Evaluation after GnRHa discontinuation (yr)		6.33 (1.6–17.83), 62	
Obesity			
BMI (kg/m^2)	23.055 (18.71–52.7), 30	21.91 (16.89–41.11), 62	0.1292
BMI SDS	0.245 (−0.96 to 7.23), 30	−0.19 (−1.89 to 4.45), 62	0.2018
WHR	0.82 (0.7–1.01), 30	0.81 (0.62–0.92), 62	0.3421
Bone density			
BMD (L1-L4, g/cm^2)	1.007 (0.808–1.489), 25	1.002 (0.76–1.371), 43	0.392[b]
Z score	−0.5 (−1.9 to 2.38), 21	−0.7 (−2.3 to 3.2), 36	0.3193
Body composition			
FM (%)	31.1 (22.4–46.7), 16	33.6 (24.1–48.7), 32	0.7110
LM (%)	65.21 (50.93–74.23), 16	62.45 (48.08–71.78), 32	0.5958
Ovarian function			
Age at menarche (yr)	11.835 (7–16.5), 30	13 (8.58–17), 62	0.0088[a]
MC (d)	30 (27–45), 28	28 (20–40), 59	0.0939
Days of bleeding	5 (3–10), 28	6 (3–10), 59	0.0548
Irregular menstrual cycles (%)	39.3 (11/28)	25.4 (15/59)	0.1870
Referred dysmenorrhea	35.7 (10/28)	47.5 (28/59)	0.3022
Use of contraceptives (%)	28.6 (8/28)	18.6 (11/59)	0.2951
Pregnancies	3.5 (1/28)	1.75 (1/57)	0.553
Cinical hyperandrogenism			
Acne (%)	17.9 (5/28)	30.5 (18/59)	0.1426
Ferriman-Gallwey score	6.5 (4–18), 28	5 (4–15), 59	0.0890
Indices of PCOS			
Ovarian volume (ml)	7.21 (3.1–18.8), 28	6.98 (2.01–20), 52	0.2222
Ovarian volume greater than10 ml (%)	21.42 (6/28)	5.76 (3/52)	0.034[a]
Number of follicles 12 or greater (%)	25 (7/28)	11.5 (6/52)	0.139
LH to FSH ratio	1.11 (0.24–5.29), 27	0.61 (0.21–5.2), 53	0.0008[a]
LH (mIU /ml)	4.76 (1.3–10.1), 27	3.3 (0.7–20.7), 53	0.0159[a]
FSH (mIU /ml)	5 (0.7–11.4), 27	5.5 (0.5–9.8), 53	0.1360
Testosterone (ng/ml)	0.495 (0.08–1.5), 27	0.4 (0.08–2.61), 53	0.1292
Delta 4 (ng/ml)	2.4 (0.2–5.4), 27	2.2 (0.7–4.8), 53	0.2266
DHEAS (μg/ml)	1730.5 (490–4836), 27	1949 (796–6340), 53	0.4132
PCOS prevalence (%)	32.14 (9/28)	11.11 (6/54)	0.0195[a]
Additional US findings			
Uterine volume (ml)	48.4 (23.79–81.14), 27	43.62 (14.7–80.14), 39	0.3511

US, Ultrasound.

[a] All results with a two-sided $P \leq 0.05$ are considered statistically significant.

[b] The result is height adjusted.

cating a height gain of 7 cm, whereas using the accelerated standards the PAH of 158.2 cm is comparable with the FH achieved (158.5 cm). Hence, this has to be taken into consideration when the ΔFH-PAH is used as a criterion of efficacy in any intervention for growth improvement in ICPP subjects.

The BMI pattern during and after GnRHa treatment in patients with CPP or early puberty is a debated point. Some authors report a significant increase in BMI during and after GnRHa treatment (12, 13), others report no effect (9–11), whereas in one study a reduction in BMI was observed (34). In our study, the median BMI and median BMI SDS of GnRHa-treated patients with ICPP and ISS did not differ from that of the nontreated ones in adulthood. In the group of GH-deficient patients, although median BMI and median BMI SDS did not differ at start of therapy, in adulthood the ones treated only with GH were more obese than those treated with combined GnRHa plus GH. We attributed this difference to the longer treatment period with GH in those receiving the GnRHa and GH combination.

Although suppression of ovarian activity has been associated with BMD reduction during GnRHa treatment (14, 16, 17), recent studies have shown restoration of BMD after cessation of treatment (9–11, 15, 18). In our study, BMD values adjusted for height at final evaluation (1.6–17.8 yr after GnRHa discontinuation) did not differ between GnRHa-treated and nontreated patients. Moreover, body fat mass in adulthood, determined by DXA, did not differ between GnRHa-treated and the corresponding nontreated subjects in all three groups, suggesting that GnRHa treatment does not lead to increased fat mass accumulation. Published data on body composition of GnRHa-treated patients with precocious or early puberty

during treatment or close to the GnRHa discontinuation suggested an increase in fat mass (12, 14). Heger *et al.* (10) reported percent FM (37%) in 50 adult women who had been treated with GnRHa for precocious puberty, a value that is higher than ours in all subgroups. Nevertheless, a nontreated group was not included in that study.

In all groups, menarche occurred at a median interval of 1 yr after discontinuation of GnRHa treatment. The age at menarche of GnRHa-treated patients was higher than that of the nontreated ones, which is an expected finding. MC characteristics, use of contraceptive drugs, and presence of acne did not differ between the subgroups of each category, being in accordance with previous reports showing normal ovarian function after discontinuation of GnRHa treatment (10–12, 19, 20).

In our study the ovarian volume of nontreated patients with ICPP in early adulthood was greater than that of GnRHa-treated patients, a finding different from that observed by other authors (10, 28). Moreover, nontreated patients with ICPP had higher Ferriman-Gallwey scores, LH values, and LH to FSH ratios than GnRHa-treated patients.

Literature data with respect to the occurrence of PCOS in patients with CPP are quite heterogeneous. Boepple (35) observed PCOS in approximately half of the patients treated with GnRHa, whereas Bridges *et al.* (36) reported a prevalence of 24% of PCOS during GnRHa therapy compared with only 2% in an age-matched control group. Baek-Jensen *et al.* (37) did not observe PCOS during or after treatment with GnRHa. Heger *et al.* (10) found no increased incidence of PCOS in GnRHa-treated patients with CPP compared with the normal population. We must note that the criteria used for PCOS diagnosis were not uniform in the above studies. Very recently Franceschi *et al.* (38) reported 32 and 30% prevalence of PCOS in young women with ICPP treated with GnRHa, according to the Rotterdam (29) and Androgen Excess Society consensus criteria (39), respectively, but no control group was included. In our study, the prevalence of PCOS (defined by the 1990 National Institutes of Health sponsored conference criteria) in girls with ICPP treated with GnRHa was comparable with that in the untreated (17.2 and 30.8%, respectively, $P = 0.32$). Nevertheless, when the entire cohort was divided in GnRHa-treated and nontreated, 32.1% of the nontreated and 11.1% of the GnRHa-treated patients had PCOS ($P = 0.02$). The higher incidence of PCOS in nontreated subjects persisted after adjusting for BMI SDS and age of evaluation, but it was not present after adjusting for time since menarche. However, a selection bias cannot be excluded, namely those who were motivated to come from the nontreated group had more problems related to ovarian dysfunction.

In conclusion, in this long-term follow-up study, it was shown that GnRHa treatment in childhood and early adolescence does not adversely affect BMI, BMD, body composition, and ovarian function, at least in late adolescence and early adulthood. When GnRHa treatment is initiated in girls with ICPP at a median age of about 8 yr, there is no increase in FH. There is no evidence that GnRHa treatment predisposes to PCOS development or menstrual irregularities.

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Address all correspondence and requests for reprints to: Maria-Alexandra Magiakou, First Department of Pediatrics, Aghia Sophia Children's Hospital, 11527 Athens, Greece. E-mail: mmayakou@med.uoa.gr.

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