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Ovarian suppression reduces clinical and endocrine expression of late-onset congenital adrenal hyperplasia due to 21-hydroxylase deficiency

Enrico Carmina, M.D.*
Rogerio A. Lobo, M.D.†

Universita di Palermo, Palermo, Italy, and Department of Obstetrics and Gynecology, University of Southern California School of Medicine, Los Angeles, California

Objective: To determine the effectiveness of GnRH-agonist (GnRH-a) treatment in women with late onset congenital adrenal hyperplasia.

Design: Prospective assessment of GnRH-a treatment in six women with documented late-onset congenital adrenal hyperplasia who were not preselected. Comparisons were made to previous responses in the same patients receiving dexamethasone. Eight age- and weight-matched ovulatory women served as controls.

Setting: Academic medical center.

Intervention: Baseline blood determinations before and after IV ACTH, before and after 6 months of GnRH-a treatment. Estrogen and progestin replacement was begun in all women after the 3rd month of treatment.

Main Outcome Measures: Serum 17-hydroxyprogesterone (17-OHP), gonadotropin, and androgen levels before and after GnRH-a treatment. Responses of 17-OHP and androgens to ACTH assessment of hirsutism using a modified Ferriman-Gallwey score.

Results: Gonadotropins, estrogen, androgen, and 17-OHP were suppressed with GnRH-a treatment. Levels were similar before and after estrogen and progestin replacement. Responses of 17-OHP after ACTH were blunted but still were elevated compared with responses in controls. Ferriman-Gallwey scores decreased significantly (-8 ± 1; mean ± SE). This response was greater than that observed previously with 6 months of dexamethasone (-2 ± 0.3).

Conclusions: Suppression of the ovary with GnRH-a treatment was beneficial in these patients with late-onset congenital adrenal hyperplasia. An ovarian influence on the clinical and biochemical findings of the disorder is suggested. Fertil Steril 1994;62:738–43

Key Words: GnRH-agonist, congenital adrenal hyperplasia, dexamethasone, hirsutism

Adult or late-onset congenital adrenal hyperplasia (CAH) due to mild 21-hydroxylase deficiency results in well-characterized steroid abnormalities. Androgen levels and 17-hydroxyprogesterone (17-OHP) are elevated, although plasma cortisol and ACTH are normal (1–8). However, most patients with this mild adrenal enzymatic deficiency have characteristics that overlap with those of patients with polycystic ovary syndrome (PCOS). The ovaries characteristically are polycystic, androgen levels are elevated equally, and there usually are abnormalities in LH secretion (9, 10). We had suggested earlier that the LH abnormalities may be explained, at least in part, by the common finding of elevated unbound E_2 in both patients with CAH and PCOS (10).

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* Cattedra di Endocrinologia, Universita de Palermo.

† Division of Reproductive Endocrinology, Department of Obstetrics and Gynecology, University of Southern California School of Medicine

‡ Reprint requests: Rogerio A. Lobo, M.D., Department of Obstetrics and Gynecology, Women's and Children's Hospital, Room 1M2, Los Angeles County+University of Southern Medical Center, 1240 North Mission Road, Los Angeles, California 90033 (FAX: 213-226-2850).

Although corticosteroid suppression therapy characteristically has been used for this disorder, other agents, such as cyproterone acetate, have been used successfully for the treatment of hirsutism in these patients (11). We have also observed that dexamethasone (DEX) treatment is not highly effective for the treatment of hirsutism in PCOS, despite normalization of androgen levels in most patients (12). Because there may be a significant ovarian contribution to the abnormal steroid profiles of patients with CAH, we postulated that ovarian suppression alone with the GnRH agonist (GnRH-a) may be an effective treatment. To this end, we have treated patients with well-characterized CAH with a GnRH-a, Decapeptyl (Ipsen, France) to determine efficacy and to compare these results with treatment using DEX.

MATERIALS AND METHODS

Six hirsute female patients, aged 16 to 28 years (mean ± SE; 22.3 ± 1 years and mean body mass index 23.5 ± 1.0), affected by CAH were studied. The hormonal profiles of these patients were compared to those of eight age- and weight-matched controls. These ovulatory women had no findings of hyperandrogenism and had normal blood levels of androgens and 17-OHP as depicted below. The diagnosis of CAH was made by the finding of increased early morning levels of 17-OHP (>5 ng/mL [>15 nmol/L]) and exaggerated 17-OHP responses to IV ACTH 1–17 (17-OHP peak >10 ng/mL [30 nmol/L], at 60 minutes) (3–5, 7, 13). All the patients were treated previously with DEX at a mean dose of 0.5 mg/d for ≥6 months (range, 1 to 3 years) but stopped DEX treatment for ≥6 months before entering into the study protocol. No patient was considered a poor responder on DEX, no patient was selected specifically for this study, and no patients who had been treated were excluded specifically from participating in this protocol. Nevertheless, all these patients had features overlapping with those commonly associated with PCOS, including peripubertal onset of symptoms, cystic ovaries, and, as a group, increased serum LH and increased LH:FSH ratios (Table 1).

Study Design

All patients and controls were studied between days 5 and 8 of a normal cycle or after progestin-induced menses in the case of patients. Studies were carried out between 8:00 and 10:00 A.M. All patients were treated with GnRH-a (Decapeptyl) at a dose of 3.75 mg IM every 28 days, starting on day 1 of spontaneous menses, for 6 months. Starting with the 4th injection, 0.625 mg conjugated equine estrogens were administered on days 1 to 21 of each month. In addition, 10 mg medroxyprogesterone acetate was given on days 12 to 21.

Assays

Before treatment and after 3 and 6 months (between days 5 and 8), fasting blood samples were obtained between 8:00 and 9:00 A.M. for the following parameters: LH, FSH, E_2, total T, unbound T, androstenedione (A), DHEAS, 17-OHP, cortisol, and ACTH. The 17-OHP and A responses to IV ACTH were also evaluated before treatment and again at 6 months (blood samples at 0, 60, and 120 minutes). In four patients, serum 11β-hydroxyandrostenedione also was determined.

Serum LH, FSH, E_2, T, unbound T, DHEAS, A, 11β-hydroxyandrostenedione, and 17-OHP were evaluated by well-established RIA methods (14–17). Steroid assays included extraction and celite chromatography. In the LH and FSH assays, the standard used was LER 907, which was referenced to the Second International Reference Preparation. In all assays, intra-assay and interassay coefficients of variation did not exceed 6% and 13%, respectively. Adrenocorticotropic hormone levels in plasma was measured by a commercial RIA kit (Radioassay Systems Laboratories, Inc., Carson, CA). Cortisol was determined by a commercial RIA kit (Mallinckrodt Diagnostica, Dietzenbach, Germany). For these assays, intra-assay and interassay coefficients of variation did not exceed 8% and 12%, respectively. Hirsutism was assessed by a modified Ferriman-Gallwey score (18).

Data Analyses

The data from this study are reported as means ± SE. Student's *t*-test, with log transformation for hormonal measurements, was carried out for within-group changes as well as analysis of variance for multiple comparisons.

RESULTS

Demographic and hormonal data for the patients with CAH are depicted in Table 1. Serum LH and

Table 1 Clinical and Endocrine Features of CAH Patients

Patient	Age	Basal body index	Hirsutism (Ferriman-Gallwey scores)	Basal 17-OHP*	Peak 17-OHP†	LH‡	LH:FSH ratio
				nmol/L		*mIU/mL*	
1	34	21.6	15	45.4	130.1†	12.8	2.0
2	34	23.0	12	61.7	181.5†	20.0	2.0
3	20	22.5	12	31.2	100.5†	16.0	2.7
4	16	20.8	18	48.4	109.0†	10.5	1.8
5	26	26.2	15	16.3	37.8†	18.1	2.0
6	24	27.0	12	82.5	151.3†	25.0	2.3
Mean ± SE	22.3 ± 1.5	23.5 ± 1.0	14 ± 1	47.6 ± 9.5§	118.4 ± 20.2§	17.1 ± 2.1§	2.1 ± 0.1§
Controls (n = 8)	21.8 ± 1.0	23.1 ± 0.4	—	2.0 ± 0.5	6.0	9.4 ± 1.0	1.1 ± 0.1

* Conversion factor to SI unit, 0.331.
† Peak 17-OHP response to ACTH.
‡ Conversion factor to SI unit, 1.00.
§ $P < 0.01$.

17-OHP were significantly elevated. In addition serum T, unbound T and A were elevated ($P < 0.01$); whereas FSH, E_2, DHEAS, cortisol, and plasma ACTH were normal (data not depicted).

Gonadotropin-releasing hormone agonist treatment significantly ($P < 0.01$) reduced levels of serum LH and E_2 after 3 months in all patients. Serum LH levels were suppressed <2 mIU/mL (<2 IU/L) and serum E_2 to <30 pg/mL (<110 pmol/L). With the addition of estrogen + progestin at 6 months, LH levels remained suppressed. Serum FSH levels were significantly ($P < 0.01$) reduced only after the addition of estrogen + progestin to GnRH-a treatment.

Serum T, unbound T, and A were significantly ($P < 0.01$) decreased by GnRH-a treatment whereas DHEAS levels were unchanged after 6 months. No significant differences in serum androgens were observed between GnRH-a alone at 3 months and after GnRH and estrogen + progestin (6 months). Compared with controls, total T and A still were elevated whereas unbound T and DHEAS were similar to levels in controls.

Basal serum 17-OHP was significantly ($P < 0.01$) reduced with GnRH-a therapy as were the responses of 17-OHP and A to ACTH ($P < 0.05$) (Fig. 1). However, basal serum 17-OHP levels and the maximum responses of 17-OHP after ACTH still were significantly ($P < 0.01$) higher than these parameters in normal women. In four of the six patients after GnRH-a treatment, strict diagnostic criteria still were met (3–5, 7, 13). In the other two, 17-OHP responses were intermediate. As a group, after GnRH-a, the maximum responses of 17-OHP were 6.6 to 13 ng/mL (20 to 39 nmol/L) and 17-OHP responses were 4.1 to 6.7 ng/mL (12.5 to 20.3 nmol/L). Figures 2 and 3 compare the responses of these patients after GnRH-a treatment with previous responses observed with DEX treatment.

Gonadotropin-releasing hormone agonist treatment significantly improved hirsutism after 6 months and Ferriman-Gallwey scores decreased from 16.4 ± 1.0 to 8.4 ± 1.0. The decrease in Ferriman-Gallwey scores after the GnRH-a was significantly greater than that observed in these patients previously after DEX alone (−8 ± 1 versus −2 ± 0.3; $P < 0.01$) (Fig. 2).

With DEX, the percentage suppression of DHEAS and of 17-OHP was greater than with

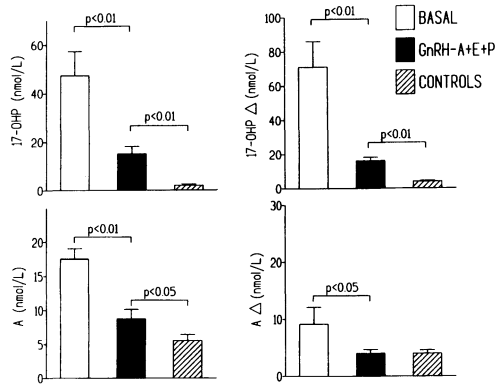

Figure 1 Serum 17-hydroxyprogesterone and the incremental response of 17-OHP after ACTH (17-OHP Δ) and A and its response after ACTH (A Δ) in patients before (□) and after (■) estrogen and progestin + GnRH-a therapy and in controls (▨). (Conversion factor of nmol/L to ng/mL 0.331 for 17-OHP and 0.286 for A).

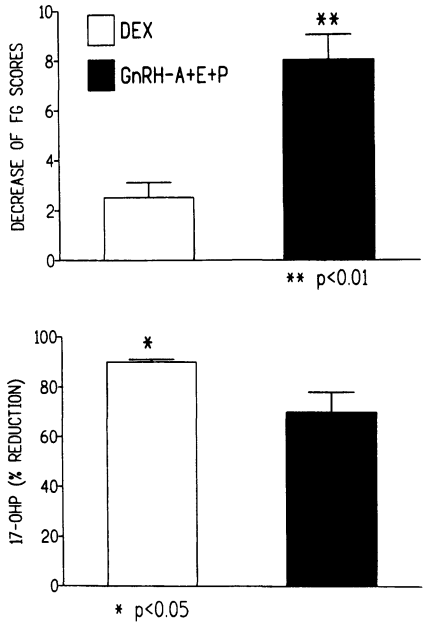

Figure 2 Comparisons of the decrease in Ferriman-Gallwey (FG) scores and the percentage reduction in 17-OHP with DEX (□) versus estrogen and progestin + GnRH-a (■). Statistical differences from the other group, $*P < 0.05$; $**P < 0.01$.

GnRH-a (Fig. 4). The suppression of unbound T, on the other hand, was greater with the GnRH-a (Fig. 3).

11β-Hydroxyandrostenedione was elevated (>2 ng/mL [>6.9 nmol/L]) in the four patients in which it was measured ([3.8 ± 0.3 ng/mL] 13.3 ± 1 nmol/L). After GnRH-a therapy, values were unchanged (3.4 ± 0.5 ng/mL [11.9 ± 1.7 nmol/L]).

DISCUSSION

The diagnosis of late-onset CAH had been somewhat controversial until the genetic basis for the disorder was established (1, 4) and firm diagnostic criteria were accepted (3–5, 7, 13). Nevertheless, there are many acknowledged similarities between these patients and those with PCOS. The findings of elevated LH and PCOS are extremely common. We suggested (10) that at least some of the LH findings in CAH may be due to an elevation of estrogen, specifically unbound E_2.

Because many hirsute patients with PCOS have been found to benefit from GnRH-a therapy (19), we carried out this trial to determine if ovarian suppression may be beneficial for these patients who have an adrenal disorder. We were encouraged to do this because therapies other than corticosteroid suppression (e.g., cyproterone acetate) have been found to be useful for CAH (11). For this trial, six patients were studied who previously had received 6 months of DEX but who had elected to stop treatment. This was not because of a perceived poor response to DEX. No patient was selected specifically because it was thought that a better response might occur with a GnRH-a. All these women had been off treatment for ≥6 months before enrollment in this study. Nevertheless, the characteristics of these women (Table 1) were such that they all closely resembled patients with PCOS. Although some other patients with CAH may not have such typical features of PCOS, a recent study suggested that virtually all patients with CAH have polycystic ovaries (20).

Our results suggest that GnRH-a treatment may be extremely effective for at least some patients with late-onset CAH. Androgen levels were suppressed and hirsutism was decreased significantly. Indeed, the clinical responses were better than those of prior DEX treatment. Of interest was the substantial decrease in 17-OHP. This was not to the same extent as with prior DEX treatment, but significant suppression was observed. After GnRH-a, however, responses to ACTH, although decreased, still were elevated over values of controls. An intrinsic adrenal abnormality still could be diagnosed in four of the six patients by strict criteria, but all the responses still were elevated compared with controls. Moreover, DHEAS levels were not suppressed. In four patients, we also measured

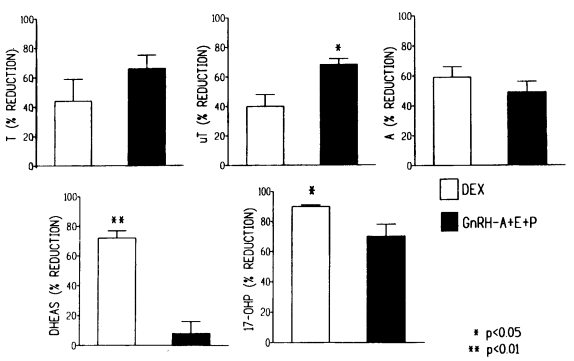

Figure 3 Comparisons of the percentage reduction in T, unbound T, A, DHEAS, and 17-OHP in patients treated with DEX (□) and estrogen and progestin + GnRH-a therapy (■). Statistical differences from the other group, $*P < 0.05$; $**P < 0.01$.

11β-hydroxyandrostenedione, another excellent marker of adrenal androgen secretion (17). In these patients, 11β-hydroxyandrostenedione was unchanged, suggesting that the GnRH-a did not directly suppress the adrenal. Our findings therefore are most compatible with the notion that GnRH-a therapy was beneficial for these patients because of its suppression of the ovary. Because only six patients were studied and the androgen findings in CAH are variable, we are not able to generalize our findings to all patients with CAH. More studies will be needed in the future.

In that GnRH-a treatment was successful for these patients with CAH, how then is ovarian suppression capable of affecting an adrenal enzymatic disorder? Although this question remains unanswered, the data are compatible with the suppression of a factor or factors secreted by the ovary that are involved in adrenal androgen sensitivity. In late-onset CAH, we have shown that adrenal responses to corticotropin-releasing factor are exaggerated (7) in the presence of normal plasma ACTH. These data suggest that the primary abnormality is one of enhanced adrenal sensitivity to endogenous ACTH, with a high pituitary set point for ACTH release. We, and others, showed previously that exogenous T can affect 17-OHP responses to ACTH, but that this, at least acutely, was not able to mimic the diagnosis of CAH (21, 22). More recently, we also suggested that a high estrogen status also can result in enhanced adrenal sensitivity. Nevertheless, this latter explanation would not apply here in that blunted 17-OHP responses were observed after 3 months using GnRH-a alone (low E_2 status) and this remained after 6 months with estrogen replacement.

From a clinical vantage point, our data suggest that ovarian suppression is perhaps even more beneficial than corticosteroid suppression for the complaint of hirsutism. Whether treatment with oral contraceptives alone, which causes less profound androgen suppression, would be equally efficacious remains to be determined. We began estrogen replacement after 3 months to avoid the symptomatic sequelae of hypoestrogenism. Our recent data have suggested that an additional beneficial effect on hirsutism may result (19). Therefore, whereas the hormonal data were not different between 3 months (GnRH-a alone) and with the addition of estrogen + progestin (6 months), we cannot be certain if our good results would occur with GnRH-a alone. Also unclear as yet is how long it would take after agonist treatment for the hormonal pattern to return to its original state. This will have to be the subject of future work. Indeed, the observation of such a return of ovarian function in conjunction with the anticipated progressive alterations in adrenal secretion might provide clues into the pathophysiology of the disorder.

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