Mild Adrenal and Ovarian Steroidogenic Abnormalities in Hirsute Women Without Hyperandrogenemia: Does Idiopathic Hirsutism Exist?

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To study ovarian and adrenal steroid profiles of women with idiopathic hirsutism, we compared sex steroid and basal and corticotropin (ACTH)-stimulated adrenal steroid levels before and after ovarian suppression induced by a long-acting gonadotropin-releasing hormone agonist analog (GnRH-a) in 24 hirsute women without hyperandrogenemia. Twelve healthy women served as controls for basal and ACTH-stimulated adrenal steroid levels. Serum levels of testosterone (T), sex hormone–binding globulin (SHBG), estradiol (E_2), basal and ACTH-stimulated 17-hydroxyprogesterone (17OHP), dehydroepiandrosterone (DHEA), DHEA sulfate (DHEAS), Δ^4-androstenedione (Δ^4-A), 11-deoxycortisol (S) and cortisol (F), and basal and luteinizing hormone–releasing hormone (LHRH)-stimulated gonadotropin levels were measured before and 21 days after 3.75 mg intramuscular triptorelin in hirsute women. Basal T levels and basal and ACTH-stimulated Δ^4-A, DHEA, and DHEAS levels were not different in hirsute women with respect to controls. Basal and ACTH-stimulated 17OHP was elevated, and decreased to normal after ovarian suppression with triptorelin. Although basal and ACTH-stimulated Δ^4-A levels were normal, the $\Delta\Delta^4$-A/ΔF and $\Delta\Delta^4$-A/Δ17OHP ratios were elevated and remained elevated after ovarian suppression, suggesting enhanced adrenal Δ^4-17,20-lyase activity. T, F, S, and DHEAS levels were not affected by ovarian suppression. Basal and ACTH-stimulated 17OHP and Δ^4-A, and stimulated DHEA concentrations were reduced with ovarian suppression, but their net increment and ratio to the increase of F in response to ACTH remained unchanged, reflecting the ovarian contribution to the secretion of these steroids. We conclude that idiopathic hirsute women with normoandrogenemia show an increase in ovarian secretion of 17OHP and a minimally increased adrenal Δ^4-17,20-lyase activity, suggesting that mild forms of ovarian and adrenal functional hyperandrogenism may be present in these patients with otherwise unexplained hirsutism.

THE ETIOLOGIC DIAGNOSIS of female hyperandrogenism is often difficult. During past years, the use of gonadotropin-releasing hormone analogs (GnRH-a) to stimulate[1,2] or to suppress[3] the ovary have allowed differentiation between the ovary and the adrenals as the source of androgenic excess in hyperandrogenic women. Despite these improvements in diagnosis, a significant number of women with hirsutism have normal basal circulating concentrations of the main androgens, testosterone (T), dehydroepiandrosterone sulfate (DHEAS), and Δ^4-androstenedione (Δ^4-A). These women are often considered as having idiopathic hirsutism, a condition in which an increased bioavailability of T to target tissues and an increased conversion of T to dihydrotestosterone (DHT) in the skin have been postulated as possible underlying mechanisms.[4] However, to date, these hypotheses have not been widely accepted, as unbound T and DHT are within the normal range in 33% and 50% of these women, respectively.[5] Moreover, the increase in circulating 5α-androstanediol glucuronide found in these women, initially considered a marker of 5α-reductase activity in the skin,[6] has been shown to be related to adrenal androgen precursors and to liver 5α-reductase activity.[7,8] Finally, direct examination of androgen metabolism in individual anagen hair follicles has shown mixed results,[4] leaving the cause of hirsutism in these patients unexplained.

To provide new insight into the pathophysiology of idiopathic hirsutism, in the present study we evaluated adrenal and ovarian steroid profiles in 24 women diagnosed with this disorder. On one hand, the use of a GnRH-a, by inducing a selective gonadal suppression without known effects on the hypothalamic-pituitary-adrenal axis,[9] permits identification of ovarian steroidogenic abnormalities. On the other hand, adrenal stimulation with corticotropin (ACTH), by studying basal and ACTH-stimulated steroid precursor concentrations and the relative increases of these precursors respective to the increase in their products, provide a useful tool to study the functionality of the different enzymatic pathways involved in adrenal synthesis of glucocorticoids and androgens. As will be seen, the combination of GnRH-a and ACTH testing has disclosed several mild abnormalities in both ovarian and adrenal steroidogenesis in a selected subgroup of hirsute women with otherwise normal circulating androgen concentrations.

SUBJECTS AND METHODS

Subjects

Twenty-four women with idiopathic hirsutism, defined by the presence of excessive body hair distributed in an androgen-dependent pattern, with a Ferriman-Gallwey score[10] greater than 7, normal basal T, DHEAS, and Δ^4-A plasma concentrations, and regular menstrual cycles were selected to enter the study. They were selected from a group of 66 patients referred to the Department of Endocrinology for evaluation of hyperandrogenism. Forty-two hirsute patients were excluded because of increased basal plasma concentrations of any of these three androgens in the initial evaluation. The menstrual cycle interval was evaluated on recall for every patient, and was considered regular when the interval between menses was less than 35 days for at least 6 months before the initial evaluation. None of the patients were hypertensive or had evidence of Cushing's disease or drug-induced hirsutism. Hyperprolactinemia and thyroid disease were ruled out by appropriate testing.

Twelve normal menstruating women without signs and symptoms of hyperandrogenism or a family history of endocrine diseases served as controls for basal and ACTH-stimulated steroid plasma concentrations. None of the patients or controls had been using hormonal medications,

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including contraceptive pills, for the past 6 months. Results for the control group have been previously published in part.[3]

The study was approved by the local ethics committee, and informed consent was obtained from each patient and control.

Experimental Design

Studies were performed during the follicular phase, between days 5 and 10 of the cycle. After an abdominal and pelvic ultrasonogram, the patients were submitted to the following protocol.

Basal study. Patients reported to the Endocrine-Metabolic testing room between 8 and 9 AM after an overnight fast. An indwelling intravenous (IV) line was placed in a forearm vein, and after 15 to 30 minutes, blood samples were obtained for measurement of total T, estradiol (E_2), and sex hormone–binding globulin (SHBG) levels. Immediately after taking basal samples, a 250-μg IV bolus of 1-24 ACTH (Synacthen; Ciba-Geigy, Basel, Switzerland) was injected, and blood samples were obtained at 0 and 60 minutes for measurement of plasma cortisol (F), 11-deoxycortisol (S), 17-hydroxyprogesterone (17OHP), DHEA, DHEAS, and Δ^4-A levels. After obtaining the 60-minute sample for the ACTH test, a 100-μg IV bolus of LHRH (Luforan; Serono, Madrid, Spain) was injected, and blood samples for LH and follicle-stimulating hormone (FSH) were obtained at 0 and 30 minutes. Immediately after the LHRH test was completed, a single dose (3.75 mg intramuscularly) of triptorelin (D-Trp6-GnRH, Decapeptyl; LASA-Ipsen, Barcelona, Spain) was administered.

Ovarian suppression study. Twenty-one days after triptorelin administration, in a gonadal axis suppression state,[11] basal samples for T, E_2, and SHBG were obtained from patients, and the ACTH and LHRH tests were repeated.

In control women, only the basal sampling and ACTH testing were performed, as triptorelin-induced ovarian suppression was considered unacceptable by most of them.

To evaluate the basal levels of adrenal steroids and to avoid a dexamethasone-mediated reduction of LH secretion,[12,13] no dexamethasone was administered to patients or normal women before the ACTH test. Responses to ACTH and LHRH will be identified by the steroid name followed by the time of the test when the sample was obtained (ie, DHEAS 60 for DHEAS levels at 60 minutes after ACTH injection and LH 0 for basal levels of LH). The adrenal steroidogenic profile was defined by basal and ACTH-stimulated steroid and precursor concentrations, the net increment of precursors and steroids (Δsteroid) representing the change in circulating levels from 0 to 60 minutes after acute IV administration of ACTH, and the Δprecursor/Δproduct ratios or vice versa, which represent ACTH-stimulated enzymatic activity (ie, an increase in the Δ17OHP/ΔF ratio suggests a decreased transformation of 17OHP into F, indicating a decreased 21-hydroxylase or 11β-hydroxylase activity; an increase in the $\Delta\Delta^4$-A/Δ17OHP or $\Delta\Delta^4$-A/ΔF ratios suggests that adrenal steroidogenesis is shifted to the synthesis of Δ^4-A from 17OHP, a reaction catalyzed by Δ^4-17,20-lyase, instead of the normal pathway to F synthesis from 17OHP, catalyzed by 21-hydroxylase and 11β-hydroxylase). The LHRH test was used to evaluate basal gonadotropin secretion, and the LHRH test and basal E_2 concentrations were also used to confirm suppression of the gonadal axis after triptorelin administration to patients.

All blood samples were immediately centrifuged, and serum was separated and frozen at −20°C until assayed.

Assays

T, F, S, 17OHP, DHEAS, Δ^4-A, and E_2 were determined using commercially available radioimmunoassay (RIA) kits (T, E_2, and F: Sorin Biomedica, Saluggia, Italy; S: ICN Biomedicals, Costa Mesa, CA; 17OHP: Immunochem, Carson, CA; DHEAS: Diagnostic Products, Los Angeles, CA; Δ^4-A: Incstar, Stillwater, MN). The mean intraassay and interassay coefficients of variation (CVs) were as follows: T, 8.2% and 11.4%; F, 5.6% and 8.7%; S, 7.1% and 12.6%; 17OHP, 8.2% and 11.7%; DHEAS, 6.4% and 7.6%; Δ^4-A, 7.9% and 11.1%; and E_2, 5.3% and 10.7%. DHEA level was measured by RIA after extraction with dichloromethane (Diagnostic Products) with intraassay and interassay CVs of 8.6% and 12.4%, respectively. SHBG level was measured by immunoradiometric assay (IRMA) (Orion Diagnostica, Espoo, Finland) with 4.1% and 6.0% intraassay and interassay CVs. The free androgen index (FAI) was calculated using the formula, FAI = T (nmol/L) × 100/SHBG (nmol/L). LH and FSH levels were measured by IRMA (CIS Bio International, Gif-sur-Yvette, France) with intraassay and interassay CVs of 4.3% and 9.4% and 3.5% and 8.7%, respectively. All hormone determinations for each individual were performed in duplicate within a single assay.

Ultrasonography

Transparietal abdominal and pelvic ultrasonography was performed in every patient using a Toshiba 3.75-MHz transducer (Tosbee SSA-240; Toshiba Medical Systems, Tokyo, Japan), and diagnosis of polycystic ovaries was based on published criteria.[14]

Statistical Analysis

Results are expressed as the mean ± SD in the text and tables and as the mean ± SE in the figures. To compare mean values in hirsute women before and after ovarian suppression versus the control group, one-way ANOVA was used, followed by Dunnet's post hoc procedure to separately compare the mean steroid values before and after ovarian suppression with the values of the control group.[15] Patients' hormonal parameters before and after ovarian suppression were compared by the paired two-tailed *t* test. *P* less than .05 was considered significant.

RESULTS

Clinical Characteristics, Ultrasonographic Findings, LH:FSH Ratio, and Confirmation of Triptorelin-Induced Gonadal Axis Suppression

The group of hirsute women had a mean age of 24 ± 6 years (range, 16 to 40), a body mass index of 24 ± 5 kg/m^2, and a Ferriman-Gallwey score of 14 ± 5. The control group had a mean age of 27 ± 4 years (range, 23 to 38) and a body mass index of 23.1 ± 6.0 kg/m^2. Polycystic ovaries were found at ultrasonography in five women (20.8%) with idiopathic hirsutism. A LH:FSH ratio more than 2 was found in one patient with ultrasonographic polycystic ovaries and one with normal ovaries. E_2 and basal and LHRH-stimulated serum gonadotropin concentrations demonstrated ovarian suppression in all patients by day 21 (Fig 1). SHBG concentrations were not affected by ovarian suppression (Fig 1). Gonadal suppression was well tolerated, and only mild symptoms of estrogen deprivation were reported by some patients during this period. All patients regained their cycle within 4 months after administration of triptorelin.

Basal Steroid Profile

T, FAI, F 0 and F 60, S 0 and S 60, Δ^4-A 0, DHEA 0 and DHEA 60, and DHEAS 0 and DHEAS 60 were not different with respect to control levels (Table 1). Only two hirsute women (8.3%) had mildly elevated FAI. When studying the patients as a group, there was an increase in mean serum 17OHP 0 and 17OHP 60, whereas mean Δ17OHP and Δ17OHP/ΔF were normal (Tables 1 and 2 and Fig 2). Although mean Δ^4-A 0, Δ^4-A

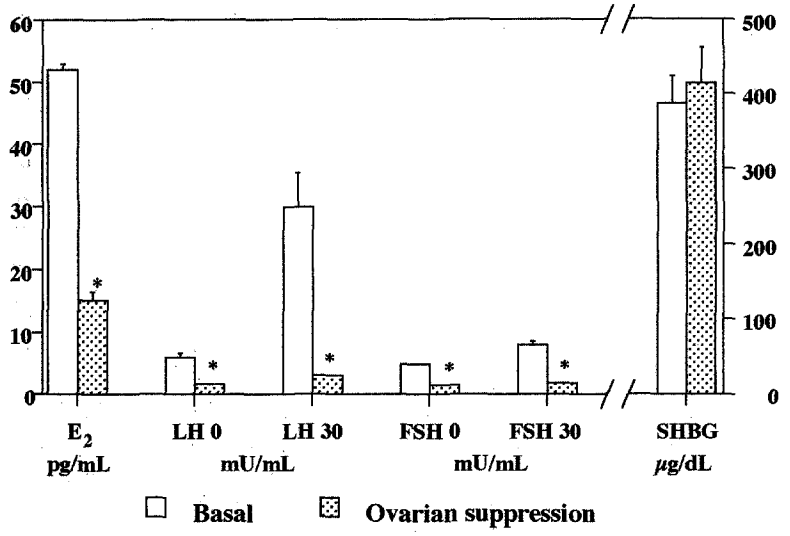

Fig 1. Effects of triptorelin administration on circulating concentrations of E_2, basal (LH 0) and LHRH-stimulated (LH 30) LH, basal (FSH 0) and LHRH-stimulated (FSH 30) FSH, and SHBG; *At least $P < .05$ in the comparison of basal and ovarian suppression states in hirsute women by paired *t* test.

60, and $\Delta\Delta^4$-A were normal, mean $\Delta\Delta^4$-A/ΔF and $\Delta\Delta^4$-A/Δ17OHP ratios were elevated (Tables 1 and 2 and Fig 3). Accordingly, when comparing individual patient data with the upper limit of the 95% confidence interval derived from the control group, 15 patients (62.5%) had an increased serum 17OHP 0, 13 (54.2%) an increased 17OHP 60, 16 (66.7%) an increased $\Delta\Delta^4$-A/ΔF ratio, and 13 (54.2%) an increased $\Delta\Delta^4$-A/Δ17OHP ratio. In fact, all these parameters were normal in only two of 24 patients.

Steroid Profile During Triptorelin-Induced Ovarian Suppression

During ovarian suppression, mean 17OHP 0 and 17OHP 60 levels of the patients were no longer different from those of the control group, as a decrease in these values with respect to the values before ovarian suppression was noted (Table 1 and Fig 2). On the contrary, and although there was a decrease within the normal range in mean Δ^4-A 0 and Δ^4-A 60 levels after ovarian suppression, mean $\Delta\Delta^4$-A/ΔF and $\Delta\Delta^4$-A/Δ17OHP ratios remained elevated (Tables 1 and 2 and Fig 3). Total T, FAI, and the remainder of the steroid precursors remained within the normal range (Table 1), and the elevated FAI present in two of the hirsute women normalized after ovarian suppression.

DISCUSSION

In the present study, we show that virtually all women with hirsutism can be demonstrated to have some underlying abnormality in androgen metabolism. All the women included in our study were considered as having idiopathic hirsutism during initial evaluation, based on the absence of severe virilization and menstrual disturbances and the absence of hyperandrogenemia. The percentage of hirsute women without basal hyperandrogenemia in our series (24 of 66 patients, 36.6%) is in line with that of previous studies,[5] in which 33% to 50% of hirsute women have normal basal androgen and SHBG characteristics. The subsequent detailed study reported here for the steroid profiles of our patients before and after ovarian suppression with a long-acting GnRH-a disclosed several abnormalities that, although mild, suggest that the hirsutism of these women can no longer be considered "idiopathic," reducing to 3% (two of 66 patients) the percentage of hirsute women with completely normal adrenal and ovarian steroid profiles. Our present results are in agreement with previous hypotheses suggesting that nearly all women with idiopathic hirsutism have underlying abnormalities in ovarian androgen production,[16] and further suggest that the abnormalities in androgen metabolism present in idiopathic hirsutism are not restricted to the ovary, originating also from the adrenal gland.

The finding of elevated 17OHP 0 levels that return to normal after ovarian suppression suggests an underlying abnormality in ovarian steroidogenesis. In the same way, we propose that the relative increase in 17OHP 60 levels found in this group of hirsute women with respect to controls should be considered a normal adrenal response superimposed on an increased 17OHP basal level of ovarian origin, as these elevated levels returned to normal with ovarian suppression and the net increment and ratios to F have been normal, excluding 21-hydroxylase hypofunction. The presence of an underlying ovarian steroidogenic abnormality is also favored by the presence of polycystic ovaries and a LH:FSH ratio more than 2 in five and two patients, respectively. None of the women studied presented 17OHP, S, and DHEA responses to ACTH characteristic of nonclassic 21-hydroxylase, 11β-hydroxylase, or 3β-hydroxysteroid dehydrogenase deficiencies.

Although Δ^4-A 0, Δ^4-A 60, and $\Delta\Delta^4$-A were not different in hirsute women with respect to controls, basal $\Delta\Delta^4$-A/ΔF and $\Delta\Delta^4$-A/Δ17OHP ratios showed a fivefold to 10-fold increase, pointing to an increased Δ^4-17,20-lyase activity in these hirsute women. The fact that these ratios remained increased after ovarian suppression suggests that the defect is restricted to the adrenal and is not influenced by ovarian function.

The increase in ovarian 17OHP secretion together with the apparent increase in adrenal Δ^4-17,20-lyase activity suggests that an enhanced cytochrome P450c17α activity, by causing very mild forms of functional ovarian and adrenal hyperandrogenism, may be one of the underlying mechanisms leading to idiopathic hirsutism. An enhanced ACTH-stimulated adrenal Δ^4-17,20-lyase activity, similar to the enhanced activity present in our patients, has been recently found by Azziz et al[17] in

Table 1. Basal and ACTH-Stimulated Steroids of Women with Idiopathic Hirsutism Before and After Triptorelin-Induced Gonadal Axis Suppression Compared with Normal Women

Hormone	Normal (n = 12)	Idiopathic Hirsutism (n = 24)
T (ng/dL)		
Before triptorelin	39 ± 14	45 ± 14
After triptorelin	NP	37 ± 13
FAI		
Before triptorelin	3.67 ± 1.96	4.33 ± 2.62
After triptorelin	NP	3.48 ± 1.73
F 0 (μg/dL)		
Before triptorelin	16 ± 6	17 ± 7
After triptorelin	NP	15 ± 6
F 60 (μg/dL)		
Before triptorelin	31 ± 8	31 ± 8
After triptorelin	NP	31 ± 10
S 0 (ng/mL)		
Before triptorelin	3.8 ± 2.2	3.5 ± 2.0
After triptorelin	NP	3.4 ± 2.2
S 60 (ng/mL)		
Before triptorelin	7.2 ± 4.1	6.4 ± 3.8
After triptorelin	NP	5.8 ± 2.8
17OHP 0 (ng/mL)		
Before triptorelin	0.8 ± 0.3	1.3 ± 0.7*
After triptorelin	NP	0.8 ± 0.5†
17OHP 60 (ng/mL)		
Before triptorelin	2.1 ± 0.9	2.9 ± 0.9*
After triptorelin	NP	2.5 ± 0.8†
DHEA 0 (ng/mL)		
Before triptorelin	8.1 ± 4.1	9.4 ± 4.9
After triptorelin	NP	8.3 ± 4.4
DHEA 60 (ng/mL)		
Before triptorelin	13.8 ± 7.0	18.7 ± 7.0
After triptorelin	NP	16.7 ± 5.5†
DHEAS 0 (ng/mL)		
Before triptorelin	1,994 ± 756	2,598 ± 820
After triptorelin	NP	2,638 ± 1,081
DHEAS 60 (ng/mL)		
Before triptorelin	1,865 ± 591	3,046 ± 1,369
After triptorelin	NP	2,890 ± 1,281
Δ^4-A 0 (ng/mL)		
Before triptorelin	2.6 ± 0.8	2.8 ± 0.8
After triptorelin	NP	2.2 ± 0.8†
Δ^4-A 60 (ng/mL)		
Before triptorelin	3.0 ± 1.0	3.8 ± 1.3
After triptorelin	NP	3.2 ± 0.9†

NOTE. Values are expressed as the mean ± SD.

Abbreviation: NP, not performed (triptorelin was not administered to normal women).

*At least $P < .05$ *v* normal women by one-way ANOVA followed by Dunnet's procedure for comparison with a control group.

†At least $P < .05$ when comparing values before and after ovarian suppression in hirsute women by paired *t* test.

approximately 15% of nonselected hyperandrogenic women. Moreover, the increased secretion of 17OHP in our hirsute women, which appeared to have an ovarian origin, is in agreement with the enzymatic dysregulation found in the ovaries of women with functional ovarian hyperandrogenism, in which abnormalities of ovarian Δ^4-17α-hydroxylase predominate over those of Δ^4-17,20-lyase.[2] 17,20-Lyase and 17-hydroxylase activities are mediated by cytochrome P450c17α. As discussed previously,[18] cytochrome P450c17α is encoded by a single gene in chromosome 10, and is expressed in both the adrenal and ovarian theca cells. Regulation of its expression could be different in the ovary versus the adrenal,[2] resulting in preferential Δ^4-17α-hydroxylase activity in the former and preferential Δ^4-17,20-lyase activity in the latter.

However, the predominant involvement of the Δ^4-pathway in functional hyperandrogenism[2] is especially intriguing, as the only enzyme known to have 17,20-lyase activity, P450c17α, primarily uses Δ^5-steroids as substrates in humans, whereas in mice both Δ^4- and Δ^5-steroids are used by this enzyme.[2] Thus, the underlying mechanism of the Δ^4-steroid abnormalities found in women with functional hyperandrogenism has not been totally elucidated, and a generalized adrenal hyperactivity rather than an enhanced P450c17α activity has been recently

Table 2. Net Increments of ACTH-Stimulated Steroids and Their Molar Ratios to the Increment of F and to the Increment of Other Steroids in Women With Idiopathic Hirsutism Before and After Triptorelin-Induced Gonadal Axis Suppression and Normal Women

Parameter	Normal (n = 12)	Idiopathic Hirsutism (n = 24)
ΔF (μg/dL)		
Before triptorelin	15 ± 7	15 ± 6
After triptorelin	NP	16 ± 7
ΔS (ng/mL)		
Before triptorelin	3.4 ± 3.3	2.8 ± 2.4
After triptorelin	NP	2.4 ± 3.4
ΔS/ΔF		
Before triptorelin	0.037 ± 0.066	0.024 ± 0.024
After triptorelin	NP	0.013 ± 0.020
Δ17OHP (ng/mL)		
Before triptorelin	1.3 ± 0.8	1.7 ± 0.9
After triptorelin	NP	1.6 ± 0.7
Δ17OHP/ΔF		
Before triptorelin	0.009 ± 0.003	0.015 ± 0.010
After triptorelin	NP	0.013 ± 0.008
ΔDHEA (ng/mL)		
Before triptorelin	5.8 ± 6.7	9.3 ± 6.5
After triptorelin	NP	8.4 ± 5.7
ΔDHEA/ΔΔ^4-A		
Before triptorelin	13.2 ± 10.8	10.4 ± 10.5
After triptorelin	NP	6.6 ± 9.4
ΔDHEA/ΔF		
Before triptorelin	0.034 ± 0.030	0.087 ± 0.070
After triptorelin	NP	0.085 ± 0.080
ΔDHEAS (ng/mL)		
Before triptorelin	−130 ± 288	449 ± 875
After triptorelin	NP	251 ± 553
ΔDHEAS/ΔF		
Before triptorelin	−0.001 ± 0.002	0.005 ± 0.014
After triptorelin	NP	0.002 ± 0.005
ΔΔ^4-A (ng/mL)		
Before triptorelin	0.4 ± 0.8	1.1 ± 1.0
After triptorelin	NP	1.0 ± 0.7
ΔΔ^4-A/Δ17OHP		
Before triptorelin	0.176 ± 0.584	0.798 ± 0.755*
After triptorelin	NP	0.738 ± 0.651*
ΔΔ^4-A/ΔF		
Before triptorelin	0.002 ± 0.006	0.011 ± 0.013*
After triptorelin	NP	0.010 ± 0.008*

NOTE. Values are expressed as the mean ± SD.

*At least $P < .05$ *v* normal women by one-way ANOVA followed by Dunnet's procedure for comparison with a control group.

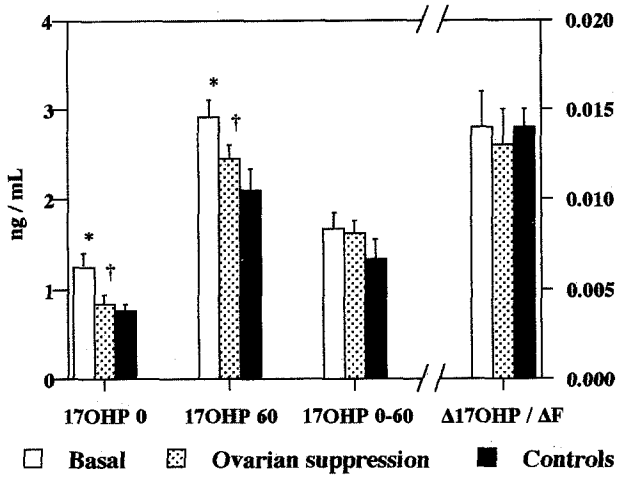

Fig 2. Responses of plasma 17OHP concentrations to ACTH (17OHP 0, basal 17OHP; 17OHP 60, 17OHP 60 minutes after a 250-μg IV bolus of 1-24 ACTH; 17OHP 0-60, net increment in 17OHP in response to ACTH; Δ17OHP/AF, molar ratio of the increase in 17OHP after ACTH stimulation with respect to the increase in cortisol). *At least $P < .05$ v normal women by one-way ANOVA followed by Dunnet's procedure for comparison with a control group. †At least $P < .05$ when comparing values before and after ovarian suppression in hirsute women by paired t test.

proposed as the cause of the adrenal component in hirsute women.[17] Although we have not completely examined the adrenal Δ^5-steroid concentrations, basal and ACTH-stimulated DHEA concentrations have not been different from the concentrations in controls, suggesting that at least adrenal Δ^5-17,20-lyase activity is not increased. Moreover, as already stated, a deficiency of adrenal 3β-hydroxysteroid dehydrogenase, which has been proposed as a frequent cause of adrenal hyperandrogenism with increased Δ^5-steroid concentrations in hirsute women,[19] was not present in our patients.

The FAI was normal in all our patients except two, in whom the increase was mild, and as a group, the FAI was not different from the control level. Thus, an increased bioavailability of T to the pilosebaceous unit does not seem related to hirsutism in these women. In any case, assuming that 5α-reductase activity could be increased in our patients, the presence of mild functional adrenal and ovarian hyperandrogenism would further contribute, by increasing the substrate to 5α-reductase, to the development of hirsutism. There is a possibility that these women could later develop hyperandrogenemia if left untreated. Unfortunately, we were unable to provide data answering this question, as all these patients underwent treatment immediately after the diagnosis was established.

Finally, the relatively high prevalence of ultrasonographic polycystic ovaries in our series could be related to an increased androgenic environment in the ovary caused by the intrinsic adrenal and ovarian enzymatic abnormalities described earlier. A prevalence of ultrasonographic polycystic ovaries in women with idiopathic hirsutism as high as 92% has been reported previously.[20] However, according to Polson et al,[21] up to 23% of apparently normal ovulatory women have polycystic ovaries on ultrasound examination, casting doubt about the functional correlate of this finding in our patients.

In conclusion, the increase in ovarian secretion of 17OHP and the adrenal hyperresponsiveness to ACTH, as assessed by enhanced adrenal Δ^4-17,20-lyase activity, suggests that women with idiopathic hirsutism might actually suffer from mild forms

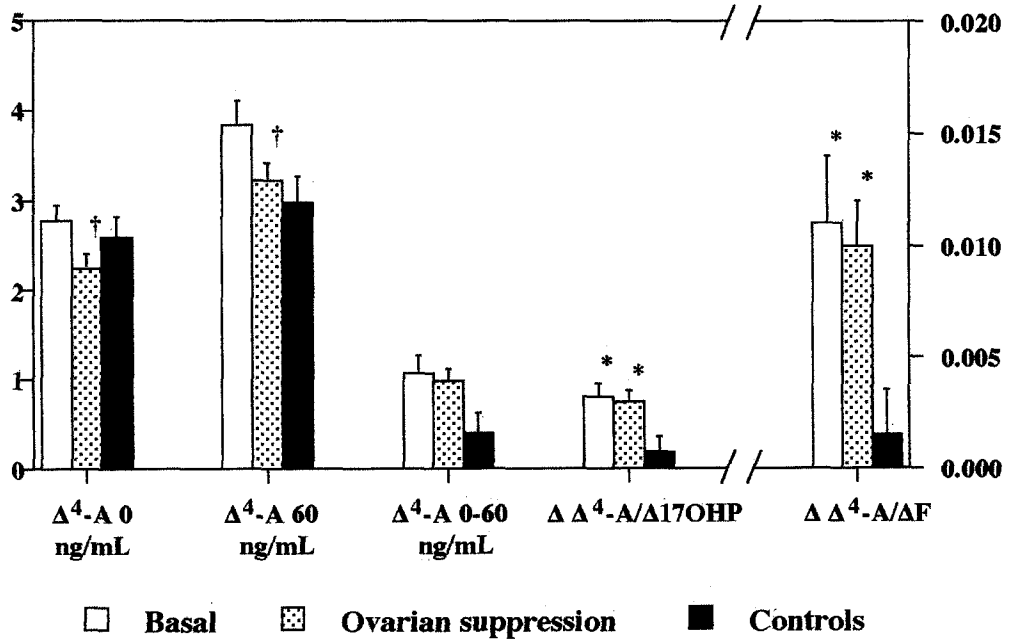

Fig 3. Responses of plasma Δ^4-A concentrations to ACTH (Δ^4-A 0, basal Δ^4-A; Δ^4-A 60, Δ^4-A 60 minutes after a 250-μg IV bolus of 1-24 ACTH; Δ^4-A0-60, net increment in Δ^4-A in response to ACTH; $\Delta\Delta^4$ -A/AF, molar ratio of the increase in Δ^4-A after ACTH stimulation with respect to the increase in 17OHP; $\Delta\Delta^4$-A/ΔF, molar ratio of the increase in Δ^4-A after ACTH stimulation with respect to the increase in cortisol). *At least $P < .05$ v normal women by one-way ANOVA followed by Dunnet's procedure for comparison with a control group. †At least $P < .05$ when comparing values before and after ovarian suppression in hirsute women by paired t test.

of functional ovarian and adrenal hyperandrogenism. Our present results may suggest that an enhanced activity of P450c17α, a key enzyme in the synthesis of androgens in the adrenal and the ovary, is present in nearly all women with functional hirsutism regardless of whether hyperandrogenemia is also present.

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