Metabolic and Hormonal Effects of Oral DHEA in Premenopausal Women with HIV Infection: A Randomized, Prospective, Placebo-controlled Pilot Study

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Key words
- endocrine effects
- DHEA
- HIV infection
- premenopausal women
- insulin sensitivity

Abstract

Women with HIV infection use dehydroepiandrosterone (DHEA) because of its potential effects on mood and energy. We examined the effects of DHEA on the hypothalamic–pituitary–adrenal and gonadal axes and on insulin sensitivity. Fifteen HIV-positive women were randomized to receive placebo (6 subjects) or oral DHEA (9 subjects). ACTH-, CRF-, and GnRH-stimulation tests were performed before and after 8 weeks of treatment. DHEA, DHEA-S, dihydrotestosterone, total testosterone, free testosterone, sex hormone–binding globulin, estrone, estradiol, cortisol, insulin, IGF-1, IGFBP-1, IGFBP-3, and adiponectin in plasma or serum were measured. There was a significant increase in DHEA ($p < 0.004$), DHEA-S ($p < 0.008$), total testosterone ($p < 0.008$), dihydrotestosterone ($p < 0.004$), androstenedione ($p < 0.04$), and estrone ($p < 0.03$) from baseline within the DHEA group but not within the placebo group. There was a significant increase in DHEA ($p < 0.0006$), DHEA-S ($p < 0.032$), total testosterone ($p < 0.01$), and dihydrotestosterone ($p < 0.005$) in the DHEA group compared with the placebo group. Oral DHEA produces significant increases in circulating DHEA, DHEA-S, testosterone, DHT, and, possibly, androstenedione and estrone levels in premenopausal women with HIV infection. In the current pilot study these hormone changes did not affect the pituitary or adrenal axis or insulin/IGF indices. Long-term studies with larger groups of patients are needed to confirm these data and to determine their clinical significance.

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Introduction

Since 1981, when HIV/AIDS was first identified, women have represented an increasing proportion of HIV-infected individuals. In the United States, the annual number of estimated AIDS cases increased 15% among women and only 1% among men from 1999 to 2003 [1]. HIV infection remains prevalent among women worldwide. Women account for nearly half of the 40 million people living with HIV (age 15–49) [1], and AIDS was the leading cause of death for black women in the 25–34 age group in 2001 [2].

DHEA is a naturally occurring adrenal hormone, a precursor to peripheral androgen and estrogen synthesis. It is one of the most abundant steroid hormones in the body. Circulating concentrations of DHEA decline with age and are reduced in numerous disease states, including adrenal insufficiency, HIV infection and depressed mood [3–15]. Some cross-sectional and longitudinal studies in individuals with HIV infection have suggested that reduced plasma DHEA and DHEA-S levels are associated with disease progression [12]. Compared with uninfected controls, HIV-positive patients have significantly lower mean plasma DHEA levels, which correlate with CD4 count [13]. Moreover, in a sample of HIV-positive men [14], initiation of antiretroviral therapy led to an increase in serum DHEA-S levels with improvement in CD4 cell count. In HIV-infected patients, DHEA replacement therapy could potentially lead to an improvement in immune status, sense of well-being, and energy level [7]. However, endocrine effects of DHEA in HIV-infected women are poorly understood and have not been previously examined in detail in controlled studies.

The aim of the present randomized, placebo-controlled pilot trial was to explore the effects of DHEA on the hypothalamic–pituitary–adrenal (HPA) axis, sex steroids, circulating insulin, adiponectin, IGF-I, IGFBP-1, and IGFBP-3 in HIV–infected, premenopausal females.

Subjects and Methods

We conducted an 8-week randomized, double-blind, placebo-controlled trial to assess primarily the effects of increasing doses (100–400 mg/day) of oral DHEA on mood [3]. As a secondary goal we assessed the effects of oral DHEA on the (HPA) axis, the hypothalamic–pituitary–gonadal axis, insulin, adiponectin, IGF-I, IGFBP-1, and IGFBP-3 in 15 HIV-infected, premenopausal women (9 in the DHEA-treated group and 6 in the placebo group) (**Table 1**).

Eligible patients were HIV positive, ranged in age from 18 to 70 years, and had a DSM-IV diagnosis of dysthymia or subsyndromal depression of at least 3 months' duration. We excluded individuals with unstable medical condition, initiation of steroids within the past 3 months, current major depressive disorder, or current substance use disorder.

Micronized DHEA in 100 mg tablets and matching placebo were provided by Belmar Pharmacy (Lakewood, CO). Subjects were randomized to receive either oral DHEA (9 subjects) or placebo (6 subjects). The initial dose of DHEA or placebo was 100 mg/day, on the basis of prior experience [3]. The dose was increased to 200 mg/day after 1 week and to 300 mg/day after 2 weeks in the absence of clinical improvement and dose-limiting side effects. After 4 weeks, an additional dose increase to 400 mg/day was permitted in the absence of clinical improvement and dose-limiting side effects.

The study protocol was approved by the Institutional Review Boards at the New York State Psychiatric Institute, the Weill Medical College of Cornell University, and the Beth Israel Medical Center, and all patients gave written consent after the risks and benefits of study participation were explained. FDA authorization was obtained for use of DHEA as an investigational drug.

At baseline and at the end of week 8, morning blood samples were drawn for the following measures: DHEA, DHT, total testosterone, free testosterone, sex hormone-binding globulin (SHBG), estrone, estradiol, cortisol, insulin, IGF-I, IGFBP-1, IGFBP-3, and adiponectin. At baseline and at the end of week 8, each patient underwent 3 stimulation tests. One hundred micrograms of synthetic luteinizing hormone–releasing hormone (LHRH, Factrel, Wyeth-Ayerst, Philadelphia, PA) was injected intravenously, and serum concentrations of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) were measured at 0, 30, and 60 min. One microgram of corticotropin (ACTH) analogue (cosyntropin, Cortrosyn, Organon, West Orange, NJ) was administrated intravenously, and serum cortisol concentrations were determined at 0, 30, and 60 min. One microgram per kilogram of corticotropin releasing factor (CRF) analogue (ACTHTREL, Ferring Pharmaceuticals, Suffern, NY) was injected intravenously, and serum cortisol and plasma ACTH levels were measured at 0, 30, and 60 min. Wilcoxon signed-rank and Mann–Whitney tests were used to analyze the data. All results were considered significant if $p < 0.05$.

Table 1 Baseline characteristics.

	DHEA group	Placebo group
number of subjects	9	6
race	Hispanic: 3 African American: 4 White: 2	Hispanic: 1 African American: 5 White: 0
AIDS diagnosis	5	4
mean age (years)	41.33 ± 10.37	44.33 ± 7.09

Results

There was a significant increase in the mean plasma concentrations of DHEA-S ($p < 0.008$), DHEA ($p < 0.004$), total testosterone ($p < 0.008$), dihydrotestosterone ($p < 0.004$), androstenedione ($p < 0.04$), and estrone ($p < 0.003$) within the DHEA group but not in the placebo group from week 1 to week 8 (**Table 2**, **Figs. 1–5**).

There was a significant increase in the mean plasma concentrations of DHEA-S ($p < 0.032$), DHEA ($p < 0.0006$), total testosterone ($p < 0.01$), and dihydrotestosterone ($p < 0.005$) in the DHEA group when compared with the placebo group (**Table 2**, **Figs. 1–4**). However, androstenedione and estrone change over time between the two groups was not statistically significant ($p < 0.59$ and $p < 0.52$, respectively, **Fig. 5**).

There was no change in baseline cortisol concentration, fasting serum insulin, SHBG, free testosterone, estradiol, adiponectin,

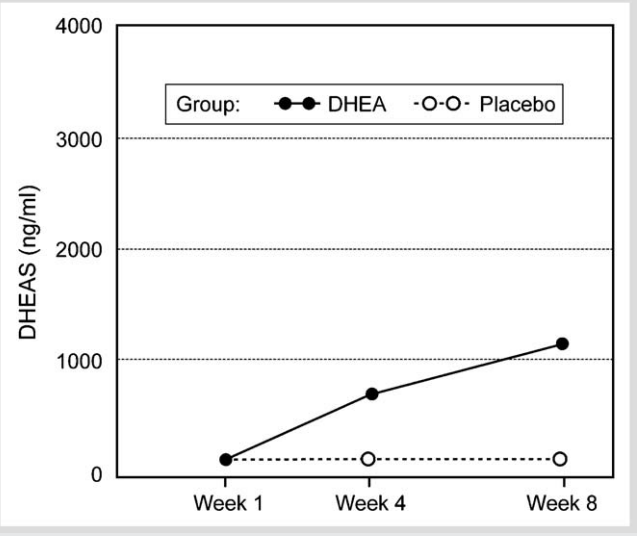

Fig. 1 DHEA-S change over time in DHEA-treated group and placebo group ($p < 0.032$ for comparison between the groups).

Table 2 Parameters that changed in the DHEA-treated group but not in the placebo group.

	DHEA group			Placebo group			P-value between
Parameter	Week 1	Week 8	P-value	Week 1	Week 8	P-value	groups
DHEA-S (ng/ml)	95.3 ± 88.0	1138.0 ± 849.0	< 0.008	104.8 ± 77.0	129.0 ± 84	0.7500	< 0.032
DHEA (ng/ml)	2.7 ± 1.7	63.3 ± 75.9	< 0.004	6.5 ± 3.6	6.5 ± 8.0	< 0.3125	< 0.0006
total testosterone (ng/ml)	0.2 ± 0.1	0.7 ± 0.6	< 0.008	0.2 ± 0.1	0.24 ± 0.15	< 1.000	< 0.01
DHT (ng/ml)	142.9 ± 67.0	907.2 ± 523.0	< 0.004	159.0 ± 67.0	199.6 ± 88.0	< 0.0625	< 0.005
androstenedione (ng/ml)	0.87 ± 0.53	3.94 ± 2.86	< 0.043	1.24 ± 0.80	2.83 ± 1.93	0.2500	0.51861
estrone (pg/ml)	144.3 ± 83.0	309.6 ± 142.0	< 0.003	143.2 ± 125.0	254 ± 213.0	< 0.0625	0.59380

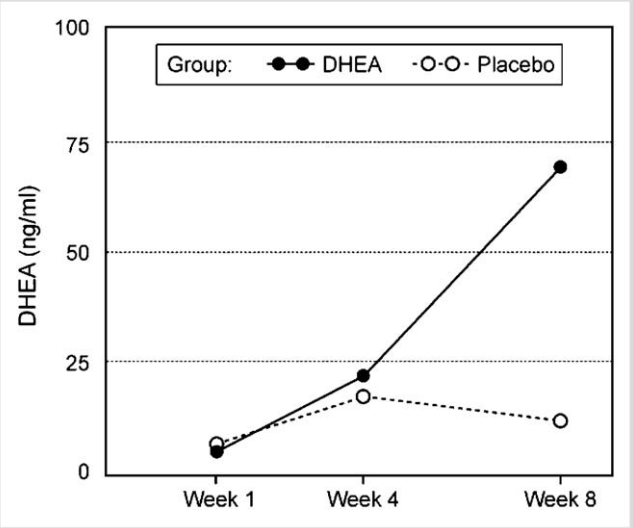

Fig. 2 DHEA change over time in DHEA-treated group and placebo group ($p < 0.0006$ for comparison between the groups).

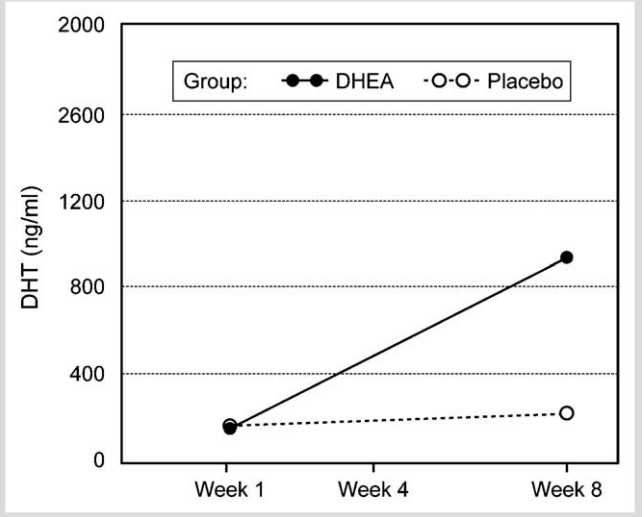

Fig. 4 DHT change over time in DHEA-treated group and placebo group ($p < 0.005$ for comparison between the groups).

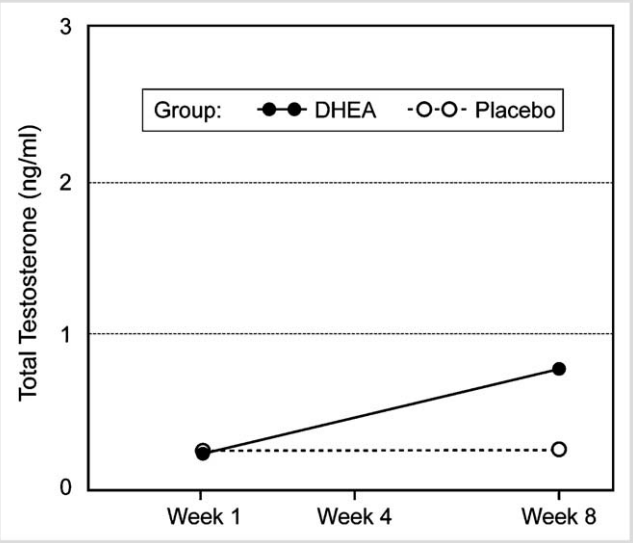

Fig. 3 Total testosterone change over time in DHEA-treated group and placebo group ($p < 0.01$ for comparison between the groups).

IGF-1, IGFBP-1, or IGFBP-3 concentrations from week 1 to week 8 in either the DHEA or placebo group (**Table 3**).

There was no significant difference between the ACTH-, CRF-, or GnRH-stimulation test results from week 1 to week 8 or between the DHEA and placebo groups (**Table 4**, **Figs. 6–10**).

Discussion

In the United States, DHEA is widely available as an over-the-counter dietary supplement. Its effects on a wide variety of conditions, such as aging, diabetes, obesity, immune dysfunction, arthritis, and depression, as well as its long-term safety, remain uncertain. Among HIV-infected individuals, DHEA is used to increase energy and muscle mass, to improve depressive symptoms, and even to improve the overall outcome of HIV infection [3,5,7,12].

We recently reported the endocrine effects of DHEA in HIV-infected men. Oral DHEA supplementation in HIV-infected men results in a significant increase in circulating levels of DHEA and DHEA-S, free testosterone, DHT, androstenedione, and estrone. DHEA therapy did not alter the overall function of the gonadal or HPA axis and had no effect on the circulating levels of major lipids, insulin, adiponectin, growth hormone, IGF-I, IGFBP-1, or IGFBP-3 [16].

This study reports a secondary analysis of the endocrine effects of oral DHEA in a group of premenopausal, HIV-infected women with mild depression. The primary outcome of the study (the effect on depression) was reported separately and revealed that DHEA was superior in the intent-to-treat analysis, where the response rate was 56% for the DHEA group vs. 31% for the placebo group [3].

In this endocrine study, we observed a significant increase in mean DHEA and DHEA-S, total testosterone, and DHT concentrations without a change in the circulating concentration of SHBG. These results differ from our previous studies in HIV-infected men, in whom we observed a significant increase in the circulating levels of free testosterone and DHT, accompanied by a decline in the circulating SHBG concentration in the DHEA-treated group [16]. Thus, the effect of oral DHEA on circulating androgen levels and on SHBG appears to be sex dependent.

Individuals with HIV infection develop insulin resistance both independently and in association with HIV-related lipodystrophy [17]. Intake of DHEA has been reported to be associated with improved insulin sensitivity in some studies [8,9]. In our study there was no change in the circulating concentrations of fasting serum insulin, adiponectin, IGF-1, IGFBP-1, or IGFBP-3.

HIV-infected individuals are at higher risk for the development of adrenal insufficiency [18]. DHEA is a precursor of cortisol, and the HPA axis hypothetically could be suppressed if a high pharmacologic dose of DHEA is used. We examined the HPA axis in our patients by using a low-dose (1 μg) corticotropin-stimulation test and a CRH-stimulation test. Our data demonstrated that there were no changes in the low-dose ACTH-stimulation test or the CRH-stimulation test results from week 1 to week 8 in either the DHEA or placebo groups.

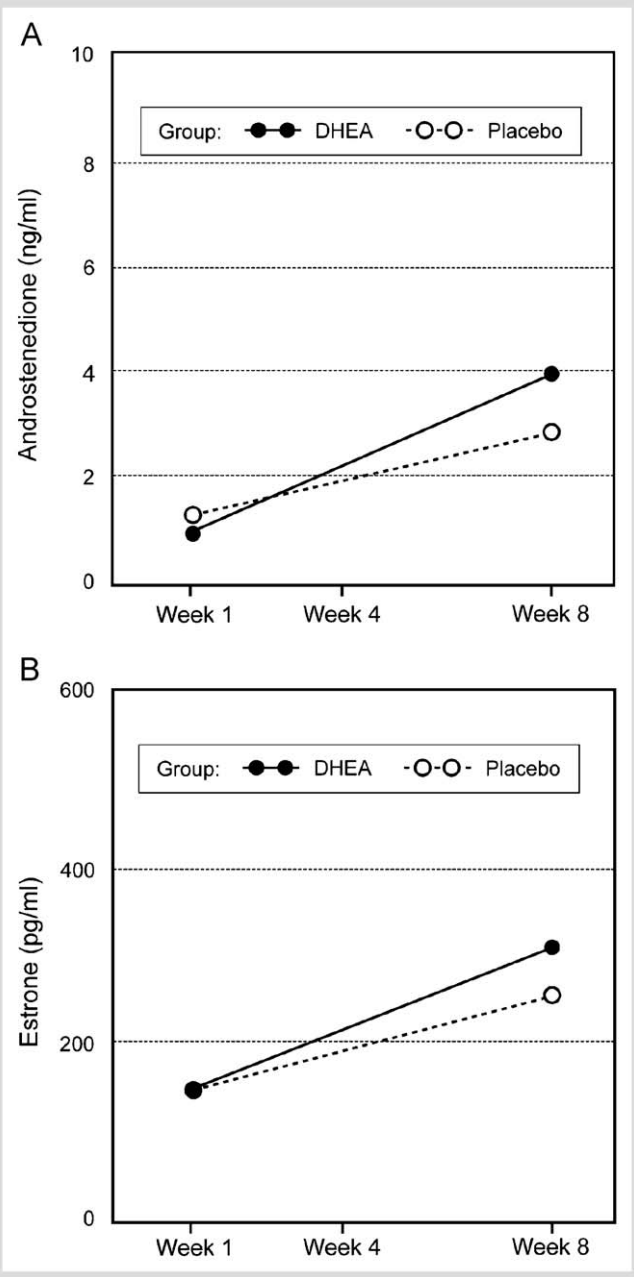

Fig. 5 Androstenedione (**A**) and estrone (**B**) change over time in the DHEA-treated group and placebo group ($p < 0.59$ for comparison between the groups for both hormones).

There is a possibility that DHEA may also suppress the HPG axis because of the conversion of DHEA to testosterone and then to estradiol through aromatization of testosterone. The GnRH-stimulation test did not show the suppression of gonadal axis in our patients.

We assessed estradiol and estrone levels because of the potential effect of DHEA on estrogen levels and the association between the risk of breast cancer and persistently elevated serum estrogens [19]. We observed that there was a significant increase in the mean plasma concentration of estrone in the DHEA group but not the placebo group. However, the differences in the plasma estrone concentrations over time between two groups were not statistically significant. Similarly, there was no significant difference in estradiol level between the two groups.

Limitations of our study are mostly related to the small number of subjects. Our collective experience in four institutions seems to indicate that it is harder to recruit women than men for HIV studies, possibly due to continued stigma associated with HIV infection in women as well as other socioeconomic factors. However, because each of our subjects was studied in great detail, some clinical implications of our study are apparent even with

Table 3 Parameters that did not change with DHEA treatment.

Parameter	DHEA group	
	Week 1	Week 8
cortisol (μg/dl)	13.8 ± 5.4	10.3 ± 7.7
fasting serum insulin (μIU/ml)	42.7 ± 32.8	40.1 ± 25.3
sex hormone–binding globulin	98.9 ± 52.4	77.0 ± 77.3
free testosterone (ng/ml)	0.8 ± 0.4	2.9 ± 2.7
estradiol (pg/ml)	175.7 ± 197.3	94.5 ± 49.7
adiponectin (ng/ml)	13.0 ± 6.3	12.9 ± 7.0
IGF-1 (ng/ml)	174.8 ± 55.1	195.4 ± 101.4
IGFBP-1 (ng/ml)	28.5 ± 33.7	25.6 ± 21.7
IGFBP-3 (ng/ml)	2190.0 ± 1413.0	2476.0 ± 1552.0
	Placebo group	
	Week 1	**Week 8**
cortisol (μg/dl)	7.6 ± 1.5	8.9 ± 3.7
fasting serum insulin (μIU/ml)	20.1 ± 21.0	38.1 ± 39.2
sex hormone–binding globulin	104.6 ± 37.2	71.1 ± 18.6
free testosterone (ng/ml)	0.7 ± 0.2	0.8 ± 0.5
estradiol (pg/ml)	110.1 ± 58.2	178.2 ± 156.1
adiponectin (ng/ml)	7.0 ± 7.3	6.4 ± 4.3
IGF-1 (ng/ml)	81.5 ± 48.8	134.7 ± 21.2
IGFBP-1 (ng/ml)	20.2 ± 20.1	15.6 ± 10.3
IGFBP-3 (ng/ml)	1578.0 ± 592.2	1783.0 ± 1002.0

Table 4 Results of stimulation tests (mean ± SEM)*.

		0 min		30 min		60 min	
		DHEA	Placebo	DHEA	Placebo	DHEA	Placebo
serum cortisol (μg/dl, low-dose ACTH-stimulation test)	week 1	13.4 ± 5.7	7.5 ± 0.2	28.1 ± 4.1	14.5 ± 2.1	22.2 ± 0.3	12.1 ± 2.9
	week 8	11.5 ± 7.2	12.3 ± 2.6	40.2 ± 22.1	16.3 ± 2.6	32.6 ± 22.4	13.7 ± 1.9
plasma ACTH (pg/ml, CRF-stimulation test)	week 1	57.1 ± 12.5	77.13 ± 9.6	64.5 ± 6.5	101.8 ± 15.3	62.9 ± 13.3	89.9 ± 10.3
	week 8	87.9 ± 19.6	57.7 ± 4.3	123.9 ± 19.3	81.7 ± 17.9	112.6 ± 20.4	77 ± 17.2
serum cortisol (μg/dl, CRF-stimulation test)	week 1	13.9 ± 2.7	7.6 ± 0.9	26.9 ± 13.2	19.3 ± 2.7	31.7 ± 12.7	20.6 ± 1.7
	week 8	10.3 ± 3.4	9 ± 2.2	23.1 ± 9.1	16.9 ± 2.0	26.5 ± 13.2	20.4 ± 3.8
plasma LH (μIU/ml, GNRH-stimulation test)	week 1	4.2 ± 1.6	9.2 ± 2.5	31.4 ± 12.2	31.1 ± 5.8	28.2 ± 11.0	31.9 ± 7.4
	week 8	3.2 ± 1.3	4.8 ± 0.9	17.4 ± 8.0	6.8 ± 2.2	18.2 ± 10.0	7.0 ± 1.5
plasma FSH (μIU/ml, GNRH-stimulation test)	week 1	3.7 ± 0.8	7.9 ± 1.9	5.9 ± 1.3	9.7 ± 1.9	6.4 ± 1.5	10.2 ± 2.1
	week 8	4.7 ± 1.5	4.3 ± 1.5	6.3 ± 1.5	5.9 ± 1.2	6.8 ± 1.6	5.7 ± 0.8

*n range = 2–6 for various parameters

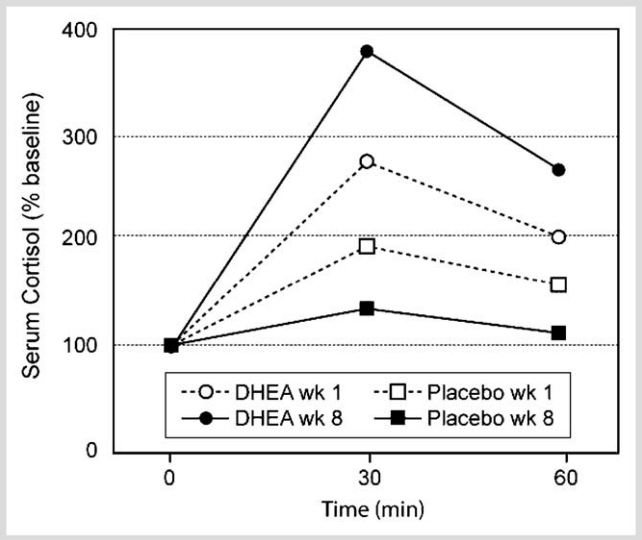

Fig. 6 Serum cortisol concentrations during 1-μg corticotropin-stimulation test.

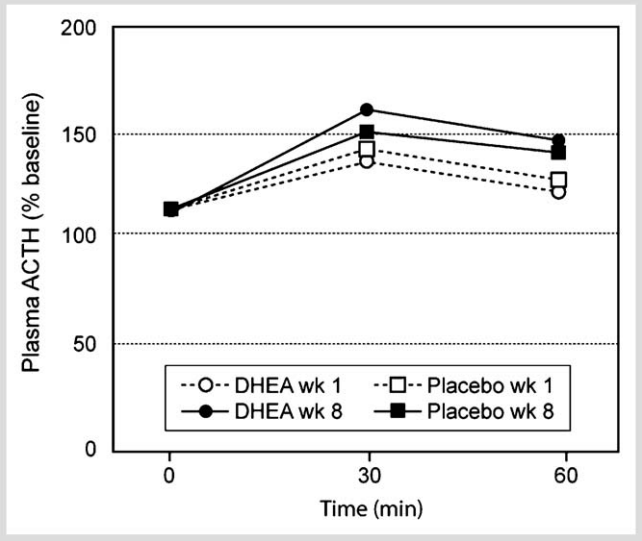

Fig. 7 Plasma corticotropin concentrations during CRF-stimulation test.

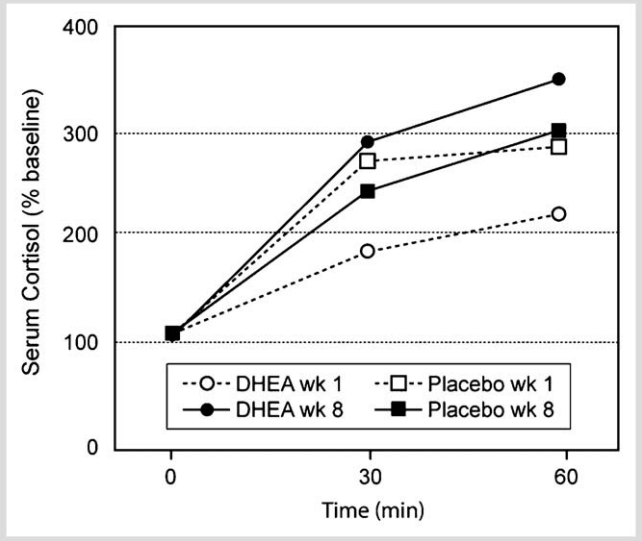

Fig. 8 Serum cortisol concentrations during CRF-stimulation test.

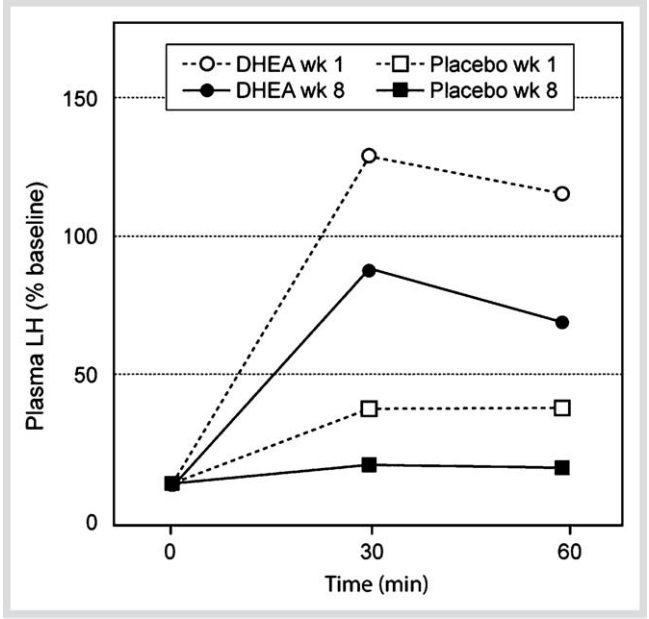

Fig. 9 Plasma LH concentrations during GnRH-stimulation test.

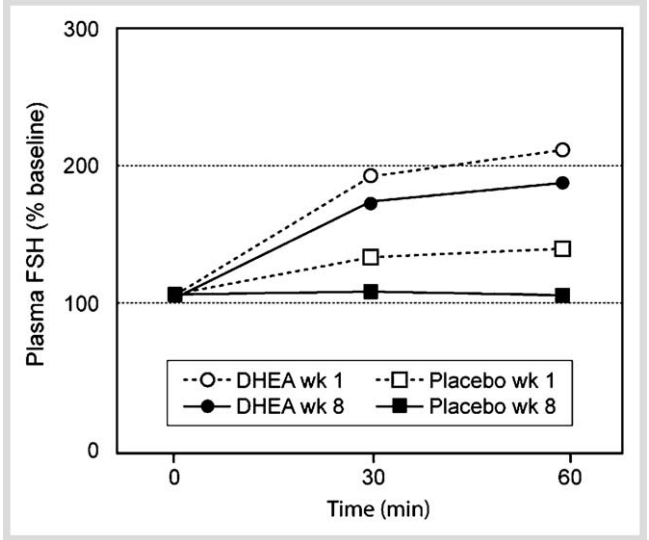

Fig. 10 Plasma FSH concentrations during GnRH-stimulation test.

the small number of subjects. First, even the relatively high doses of DHEA that we used in our study appear safe, with no effects on hepatic or renal function. Second, the increase in androgen levels observed with DHEA administration suggests that, over a period of time, androgenic effects, such as hirsutism, alopecia, or acne, may occur. The patients should be informed about the possibility of these effects, and they should be observed carefully for symptoms of hyperandrogenism.

In conclusion, in a sample of HIV-positive women in this pilot study, DHEA administration increased the circulating levels of DHEA, DHEA-S, DHT, and total testosterone. DHEA administration might also increase the circulating levels of androstenedione and estrone. DHEA administration did not have any effect on the circulating levels of cortisol, fasting serum insulin, SHBG, free testosterone, estradiol, adiponectin, IGF-I, IGFBP-1, or IGFBP-3. DHEA administration was not accompanied by significant changes in the results of ACTH-, CRF-, or GnRH-stimulation tests. However, unlike the positive results (**Table 2**, ◦ **Figs. 1–4**),

which reached statistical significance and appear to be conclusive, the negative results (**Table 3**, ◉ **Figs. 5–10**) may have been affected by an insufficient number of subjects in this pilot trial. Long-term studies with larger groups of patients are needed to confirm these data and to determine conclusively their clinical significance.

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