FERTILITY AND STERILITY®
VOL. 80, NO. 6, DECEMBER 2003

Published by Elsevier Inc.
Printed on acid-free paper in U.S.A.

Long-term low-dose dehydroepiandrosterone oral supplementation in early and late postmenopausal women modulates endocrine parameters and synthesis of neuroactive steroids

Alessandro D. Genazzani, M.D., Ph.D.,[a] *Massimo Stomati, M.D.,*[b] *Francesca Bernardi, M.D.,*[b] *Matteo Pieri, M.D.,*[b] *Lucio Rovati, M.D.,*[c] *and Andrea R. Genazzani, M.D.*[b]

University of Modena, Modena; University of Pisa, Pisa; and Rotta Research Laboratories, Monza, Italy

Objective: To evaluate the effects of a low-dose DHEA supplementation on hormonal parameters in early and late postmenopausal women.

Design: Prospective case study.

Setting: Postmenopausal women in a clinical research environment.

Patient(s): Twenty postmenopausal women were divided in two groups according to age (50–55 and 60–65 years).

Intervention(s): All patients underwent hormonal evaluation before and at 3, 6, 9, and 12 months of therapy (25 mg/d of DHEA orally). Pelvic ultrasound examination and Kupperman score were performed before and after 3, 6, and 12 months of therapy.

Main Outcome Measure(s): Plasma DHEA, DHEAS, estrone (E_1), E_2, P, androstenedione (A), T, dihydrotestosterone, 17α-hydroxyprogesterone (17-OHP), cortisol (F), allopregnanolone, β-endorphin, sexual hormone-binding globulin (SHBG), LH, FSH, growth hormone (GH), and insulin-like growth factor-1 (IGF-1) concentrations.

Results: The levels of all the steroids that derive from DHEA metabolism increased in plasma with DHEA administration. Also neurosteroids (namely allopregnanolone) and endorphin showed increased plasma levels, whereas both gonadotropins were significantly reduced. Endometrial thickness did not change throughout the study period.

Conclusions: Administration of low doses (25 mg) of DHEA positively modulates several endocrine parameters in early and late postmenopausal women, inducing the increase of the androgenic, estrogenic, and progestogenic milieu and reducing the climateric symptoms, similarly to estroprogestin replacement therapy. These data suggest that DHEA supplementation is a more effective replacement therapy than a simple "dietary supplement." (Fertil Steril® 2003;80:1495–501. ©2003 by American Society for Reproductive Medicine.)

Key Words: Postmenopause, DHEA administration, hormone replacement therapy, neurosteroids, allopregnanolone

Received June 19, 2002; revised and accepted June 17, 2003.

Reprints requests: Dr. Alessandro Genazzani, Dept. of Obstetrics and Gynecology, University of Modena, Via del Pozzo 71, 41100 Modena, Italy (FAX: 39-59-4224394; E-mail: algen@unimore.it).

[a] Department of Obstetrics and Gynecology, University of Modena.

[b] Department of Gynecology and Obstetrics, University of Pisa.

[c] Rotta Research Laboratories, Monza, Italy.

0015-0282/03/$30.00
doi:10.1016/j.fertnstert.2003.06.005

In men and women, aging is characterized by specific endocrine and neuroendocrine changes that represent a physiological adaptation of human biology to senescence. Postmenopause represents in women a peculiar period of life that is dominated by a hypoestrogenic condition that severely affects the functions of many organs and tissues, such as the skin, urogenital, skeletal, and nervous systems. Also several endocrine glands are influenced by aging, as demonstrated by the 70%–80% physiological decrease in adrenal androgen production, in particular by DHEA and DHEAS, around 70 years of age (1–5).

Recently, adrenal steroids, mainly DHEA and its sulfate ester DHEAS, have been given a

greater importance. In fact, it has been reported that the administration of DHEA greatly improves several endocrine, metabolic, and physiologic parameters both in men and women (6–9), although this has not been confirmed by all studies (10). Although DHEA supplementation is not yet considered a medical treatment, this steroid has been demonstrated to induce specific metabolic effects (6, 10, 11) and to increase both androgen and estrogen plasma levels in postmenopausal women (6, 7, 9, 10, 12, 13).

The administration of DHEA to postmenopausal women at the daily dosage of 50 mg (9, 11, 14, 15) has been shown to induce beneficial effects on quality of life and to positively affect the age-induced changes of adrenal products or peripheral products. The DHEA supplementation has shown to increase anxiolytic substances (allopregnanolone) and some neuropeptides (β-endorphin) which are crucial in modulating several central nervous system functions (9). Furthermore, patients treated with DHEA present no signs of endometrial stimulation. Although DHEA administration (50 mg/day) induces unexpected supraphysiological elevations of some steroids, mainly androgens (9), estrogen (E) levels increase to levels similar to those induced by using commercially available transdermal patches (9).

The modulation of all of these endocrine parameters suggests that the beneficial effects of DHEA in counteracting the negative phenomena related to menopause and aging may be related to the biological properties of DHEA. This molecule acts as a sort of deposit (prehormone) for the production of active metabolites. A recent report confirms such positive effect on behavior and hormonal parameters, using even lower doses of the molecule (20 and 30 mg/day) (14).

On this basis, we aimed at evaluating the effects of a 12-month DHEA supplementation (25 mg/day) on hormonal and neuroendocrine parameters, as well as on subjective symptoms in early and late postmenopausal women. This study was designed to further clarify the DHEA-induced hormonal response in (early and late) postmenopausal women, in view of considering DHEA as a putative hormonal replacement therapy.

MATERIALS AND METHODS

Subjects

We selected 20 women (age range 50–65 years) from the outpatients referred from the Department of Obstetrics and Gynecology, University of Pisa, Italy, for their postmenopausal condition. All of the patients gave their informed consent to participate in the study. The participants were healthy and none were not taking any hormone replacements.

The patients did not have thyroid, adrenal, or prolactin (PRL) disease and were not undergoing treatment for cardiovascular disease or hypertension. All patients had an ultrasound examination and a mammogram before the start of the study to exclude any organic disease.

The patients were divided in two groups according to their age: early (50–55 years old, n = 10, group A) 2–3 years postmenopausal, and late (60–65 years old, n = 10, group B) 5 or more years postmenopausal. Subjects of both groups showed a normal weight with body mass index (BMI) in the range of 20–24 (group A: BMI, 21.7 ± 0.2; group B: BMI, 22.8 ± 0.4). The study protocol was prospective and lasted 12 months. Among the subjects enrolled in the study, only 5 were mild smokers (<8 cigarettes/d).

Study Protocol

The study protocol was approved by the local Ethical Committee of the University of Pisa, and informed consent was obtained from each subject before beginning the study. All women were administered an oral dose of DHEA (25 mg, Rottapharm, Monza, Italy) every day at the same hour for 12 months.

Subjects were clinically evaluated every 3 months throughout the trial period. Blood samples were obtained from each participant at 8:00 AM, after an overnight fast, at baseline and at 3, 6, 9, and 12 months of treatment to determine the plasma levels of LH, FSH, E_2, DHEA, DHEAS, androstenedione (A), T, dihydrotestosterone, P, 17α-hydroxyprogesterone (17-OHP), allopregnanolone, estrone (E_1), sex hormone-binding globulin (SHBG), cortisol (F), β-endorphin, growth hormone (GH), and insulin-like growth factor-1 (IGF-1). All samples were immediately centrifuged and plasma was stored at −20°C until assay.

A transvaginal ultrasound examination was performed in each subject before and after 6 and 12 months of treatment to evaluate the endometrial thickness.

Kupperman score was evaluated before and after 3, 6, and 12 months of therapy. The Kupperman questionnaire included complaints for subjective vasomotor and psychological symptoms, as already described (16). Each symptom appeared on a rating scale that had a range from 0–3. The lower end of the scale for each symptom was described as "none," and the higher end, as "marked."

Assays

All hormonal determinations were carried out during the same assay. Plasma DHEA, DHEAS, A, T, dihydrotestosterone, 17-OHP, F, E_1, E_2, SHBG, LH, FSH, and GH concentrations were determined using commercially available radioimmunoassay kits (Radim, Pomezia, Rome, Italy). The intra-assay and interassay coefficients of variation (CV) were 3.8% and 6.9% for DHEA and 4.0% and 8.5% for DHEAS; 4.3% and 6.0% for A and 5.1% and 7.8% for T; 5.2% and 6.3% for 17-OHP; 3.6% and 6.2% for F and 3.8% and 7.0% for GH; 2.1% and 3.5% for E_2 and 4.4% and 6% for E_1; 2.8% and 3.3% for LH and 1.9% and 4.1% for FSH.

The IGF-1 concentrations were determined with the use of a radioimmunoassay kit (Med-genix, Fleurus, Belgium)

TABLE 1

Hormonal characteristics of early (group A) and late postmenopausal women (group B).

	DHEA (ng/mL)	DHEAS (μg/mL)	A (ng/mL)	T (ng/mL)	DHT (pg/mL)	E_1 (pg/mL)	E_2 (pg/mL)	Prog (ng/mL)	17-OHP (ng/mL)	Allopreg (pg/mL)	Cortisol (μg/L)	β-EP (pg/mL)	SHBG (ng/mL)	LH (mUI/mL)	FSH (mUI/mL)	GH (mUI/mL)	IGF-1 (mUI/mL)
Group A	3.51	0.80	1.0	0.57	34.1	34.9	18.0	0.38	0.64	224.5	222.2	22.8	9.9	33.0	76.4	0.95	86.6
	± 0.2	± 0.07	± 0.12	± 0.08	± 4.7	± 5.6	± 1.6	± 0.06	± 0.09	± 18.9	± 15.8	± 1.4	± 0.7	± 3.7	± 3.0	± 0.2	± 6.1
Group B	2.42	0.50	0.9	0.31	26.7	29.0	16.0	0.39	0.61	212.1	222.1	18.2	9.2	25.7	70.9	0.67	84.9
	± 0.2[a]	± 0.09[a]	± 0.05	± 0.07[a]	± 4.7	± 1.8	± 1.6	± 0.07	± 0.08	± 28.2	± 9.7	± 0.8[a]	± 0.5	± 3.4	± 5.6	± 0.1	± 5.1

[a] $P<.05$ vs group A.

A = androstenedione; DHT = dihydrotestosterone; E_1 = estrone; Prog = progesterone; 17-OHP = 17α-hydroxyprogesterone; Allopreg = allopregnanolone; β-EP = β-endorphin; SHBG = sexual hormone-binding globulin; GH = growth hormone; IGF-1 = insulin-like growth factor-1.

Genazzani. Low-dose DHEA supplementation and postmenopause. Fertil Steril 2003.

after acid–ethanol extraction, as described by Daughaday et al. (17). Intra- and interassay CV were 4.1% and 8.9% and the minimal detectable dose was 8.4 ng/mL, as previously reported (11).

Allopregnanolone evaluation was performed after ether extraction and chromatographic partition on Sep-Pak C18 cartridges using a radioimmunoassay method previously described (16). The sensitivity of the assay was 10 pg/tube and the intra- and interassay coefficients of variation were 7.2% and 9.1%, respectively.

The β-endorphin concentrations were determined after extraction and chromatographic partition using Sep-Pak C18 cartridges, and by using a previously described radioimmunoassay method (18). The sensitivity of the β-endorphin radioimmunoassay was 2.5 pg/mL and the intra- and interassay coefficients of variation were 6% and 9%, respectively.

Statistical Analysis

The presence of significant differences between groups was tested, after analysis of variance (one-way ANOVA), using Student's *t* test for paired and unpaired data, as appropriate. Data are expressed as mean ± SEM.

RESULTS

The hormonal characteristics of all patients in the two groups are summarized in Table 1 and are represented as mean ± SEM. As expected, younger postmenopausal subjects (group A) showed higher DHEA, DHEAS, T, and β-endorphin levels than older subjects ($P<.05$). All other endocrine parameters were determined in both groups.

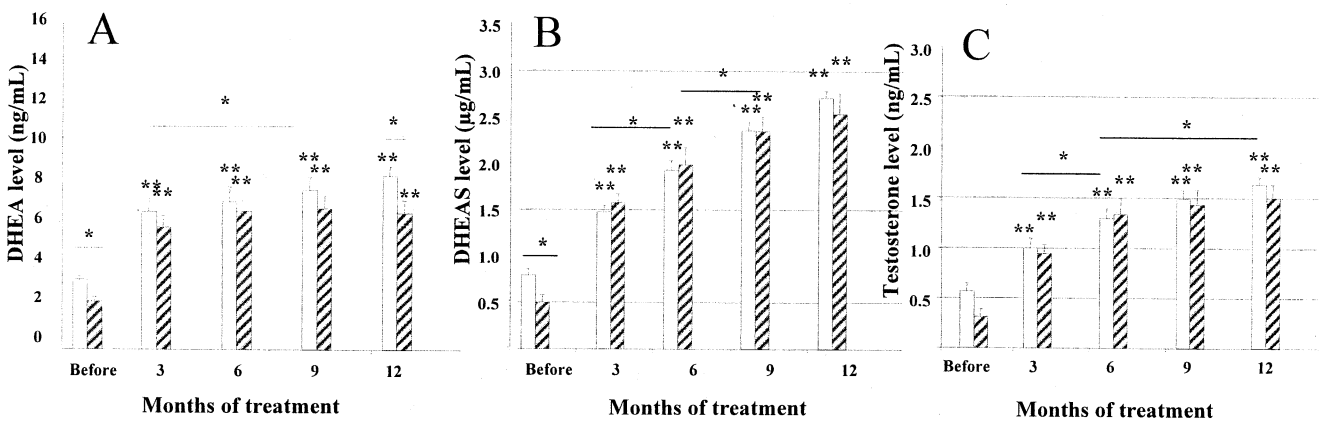
Significant changes in endocrine parameters were observed with DHEA treatment. As expected, DHEA and DHEAS levels increased significantly and progressively throughout the study interval (Fig. 1). The treatment eliminated completely the endocrine differences observed between the two groups at baseline.

Testosterone (Fig. 1), A, and dihydrotestosterone (Table 2) plasma levels increased significantly and progressively throughout the 12 months of treatment, reaching a three- to fourfold increase at the 12th month of DHEA supplementation (Fig. 1). No difference was observed between the two groups. A similar behavior was observed for plasma E_1 and E_2 levels, which increased significantly all along the study interval, reaching a three- to fourfold increase at the 12th month of treatment (Fig. 2). During the treatment no differences were found in terms of E_1 and E_2 plasma levels and in E_1/E_2 ratio between early and late postmenopausal women (Fig. 2).

Progesterone levels increased in both groups only after the sixth month of treatment and reached the highest values at the 12th month (Fig. 2). A similar behavior was observed in both groups for 17-OHP levels (Table 2). Interestingly, no changes were observed for SHBG concentrations in both

FIGURE 1

Mean ± SEM serum DHEA (**A**), DHEAS (**B**), and T (**C**) levels before and after 3, 6, 9, and 12 months of oral DHEA supplementation (25 mg/d) in early postmenopausal women (group A) (□) and late postmenopausal women (group B) (▨). *$P<.05$; **$P<.005$.



Genazzani. Low-dose DHEA supplementation and postmenopause. Fertil Steril 2003.

TABLE 2

Mean LH, FSH, GH, IGF-1, SHBG, 17OHP, A, and DHT plasma levels in early (group A) and late postmenopausal (group B) subjects before and under DHEA administration.

	Before treatment	3 months	6 months	9 months	12 months
LH (mIU/mL)					
Group A	33.07 ± 3.75	26.74 ± 3.45	22.29 ± 2.77[a]	20.31 ± 2.34[b]	18.03 ± 1.90[b]
Group B	29.70 ± 3.44	22.90 ± 3.39	19.46 ± 2.55[a]	17.43 ± 2.28[b]	16.03 ± 2.11[b]
FSH (mIU/mL)					
Group A	76.41 ± 3.92	62.34 ± 4.32[a]	56.38 ± 3.11[a]	49.48 ± 2.54[b]	40.57 ± 2.55[b]
Group B	70.90 ± 5.61	62.15 ± 5.02[a]	53.76 ± 4.85[a]	48.71 ± 4.31[b]	39.84 ± 4.54[b]
GH (ng/mL)					
Group A	0.95 ± 0.19	1.50 ± 0.21[a]	1.76 ± 0.26[b]	1.94 ± 0.20[b]	2.13 ± 0.23[b]
Group B	0.67 ± 0.08[c]	1.50 ± 0.33[a]	1.60 ± 0.20[b]	1.68 ± 0.22[b]	1.70 ± 0.24[b]
IGF-1 (ng/mL)					
Group A	89.61 ± 5.12	101.05 ± 4.40	114.92 ± 5.75[b]	117.76 ± 5.15[b]	125.80 ± 6.24[b]
Group B	91.91 ± 5.13	111.53 ± 6.18	130.90 ± 8.19[b]	146.68 ± 8.41[b]	147.98 ± 10.51[b]
SHBG (ng/mL)					
Group A	10.72 ± 0.85	9.68 ± 0.65	9.74 ± 0.60	9.80 ± 0.48	9.89 ± 0.56
Group B	8.76 ± 0.69	9.31 ± 0.47	9.73 ± 0.40	9.14 ± 0.54	10.10 ± 0.44
17-OHP (ng/mL)					
Group A	0.64 ± 0.09	0.88 ± 0.07	1.08 ± 0.06[a]	1.21 ± 0.1[b]	1.21 ± 0.1[b]
Group B	0.61 ± 0.09	0.87 ± 0.07	1.06 ± 0.13[a]	1.20 ± 0.12[b]	1.22 ± 0.17[b]
Androstenedione (ng/mL)					
Group A	1.00 ± 0.10	1.92 ± 0.21[b]	2.55 ± 0.28[b]	3.10 ± 0.10[b]	3.24 ± 0.21[b]
Group B	0.92 ± 0.05	2.39 ± 0.23[b]	3.34 ± 0.25[b]	3.58 ± 0.25[b]	3.97 ± 0.34[b]
DHT (pg/mL)					
Group A	34.10 ± 3.14	85.00 ± 8.18[b]	107.30 ± 8.71[b]	121.10 ± 7.84[b]	125.90 ± 7.71[b]
Group B	26.63 ± 4.87	79.25 ± 9.23[b]	111.75 ± 9.71[b]	123.13 ± 10.03[b]	125.63 ± 7.50[b]

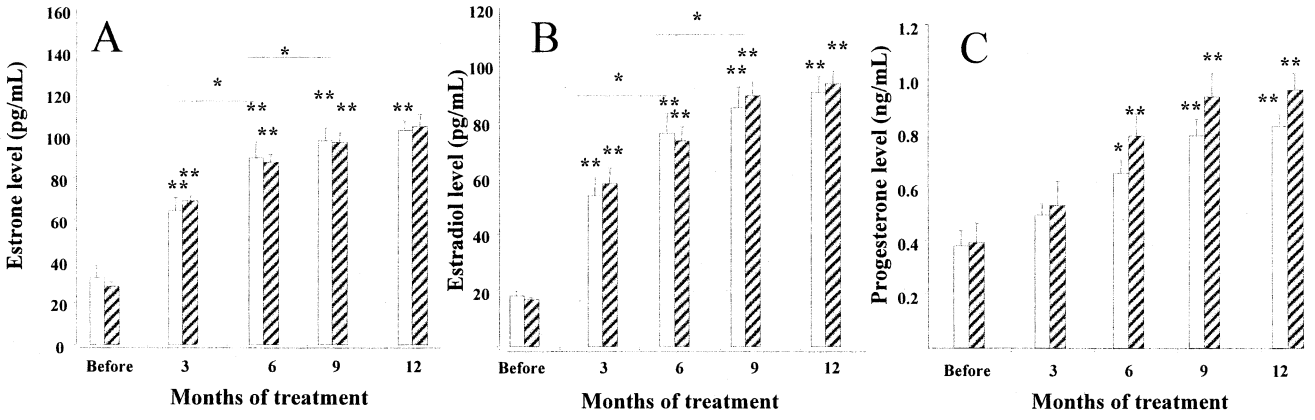
[a] $P<.05$ vs. and [b] $P<.005$ vs. before treatment; [c] $P<.05$ vs. group A.

Abbreviations as in Table 1.

Genazzani. Low-dose DHEA supplementation and postmenopause. Fertil Steril 2003.

FIGURE 2

Mean ± SEM serum estrone (E_1; **A**), E_2 (**B**), and P (**C**) levels before and after 3, 6, 9, and 12 months of oral DHEA supplementation (25 mg/d) in early postmenopausal women (□) and late postmenopausal women (▨). *$P<.05$; **$P<.005$.



Genazzani. Low-dose DHEA supplementation and postmenopause. Fertil Steril 2003.

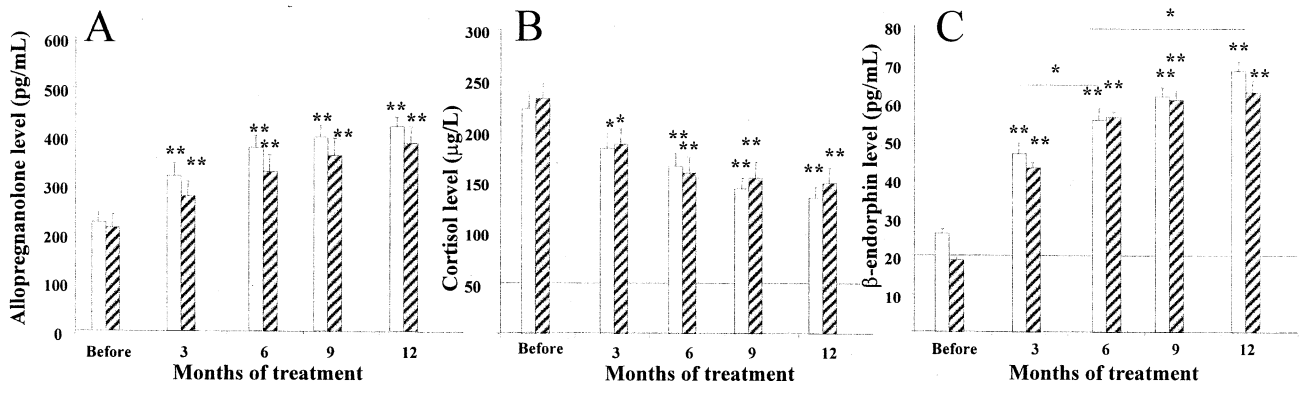
groups during the entire study period (Table 2), despite the significant changes in A and E plasma concentrations.

Allopregnanolone and β-endorphin concentrations significantly increased in both groups, reaching the maximum concentrations at the 12th month of treatment (Fig. 3). Conversely, F plasma levels showed a progressive decrease throughout the study, reaching the lowest level at the 12th month (Fig. 3). Both groups showed a significant reduction in LH and FSH plasma levels throughout the study (Table 2). The GH and IGF-1 levels significantly increased similarly in both groups, reaching the highest value at the 12th month of treatment (Table 2). No significant difference was observed between the two groups of postmenopausal women in any of these hormonal parameters.

When Kupperman's score was evaluated before treatment, younger subjects (group A) showed higher values for subjective vasomotor disturbances and psychological disturbances than older patients (group B), whereas the latter showed a higher score for psychological items (Table 3). During DHEA treatment, the Kupperman score showed a progressive and significant improvement in both groups. In fact, younger postmenopausal subjects (group A) showed

FIGURE 3

Mean ± SEM serum allopregnanolone (**A**), cortisol (F; **B**), and β-endorphin, before and after 3, 6, 9, and 12 months of oral DHEA supplementation (25 mg/d) in early postmenopausal women (group A) (□) and late postmenopausal women (group B) (▨). *$P<.05$; **$P<.005$.



Genazzani. Low-dose DHEA supplementation and postmenopause. Fertil Steril 2003.

TABLE 3

Kupperman score (mean ± SEM) for vasomotor symptoms, psychological symptoms, and total score in two groups of treatment before and 3, 6, 9, and 12 months under DHEA administration (group A: early postmenopausal women; group B: late postmenopausal women).

		Vasomotor symptoms	Psychological symptoms	Total score
	Before	20.8 ± 2.2	9.3 ± 2.1	30.1 ± 3.5
	3 months	13.6 ± 4.1[a]	6.2 ± 1.0	19.6 ± 2.1[a]
Group A	6 months	7.1 ± 2.5[a]	3.7 ± 0.4[a]	10.8 ± 1.6[a]
	9 months	6.7 ± 1.9[b]	2.6 ± 0.2[b]	9.3 ± 1.2[b]
	12 months	5.2 ± 1.0[b]	1.8 ± 0.9[b]	7.1 ± 0.9[b]
	Before	16.0 ± 2.4	8.6 ± 1.3	24.5 ± 3.8
	3 months	12.5 ± 5.1	6.9 ± 0.8	19.4 ± 2.8[a]
Group B	6 months	7.9 ± 2.5[b]	5.5 ± 1.0[a]	13.4 ± 1.8[a]
	9 months	5.5 ± 2.0[b]	4.9 ± 0.4[a]	10.8 ± 1.2[b]
	12 months	5.0 ± 1.1[b]	3.1 ± 0.7[b]	8.1 ± 0.9[b]

[a] $P<.05$ vs. before, [b] $P<.005$ vs. before.

Genazzani. Low-dose DHEA supplementation and postmenopause. Fertil Steril 2003.

lower scores for subjective vasomotor instability and psychological disturbances, and in group B subjects, for psychological disturbances (Table 3).

During DHEA administration no changes in body weight, occurrence of uterine bleeding, abnormal events, or side effects took place throughout the 12 months of therapy. Ultrasound evaluation did not show significant modifications in endometrial thickness in any of the patients of the two groups after 6 and 12 months of therapy.

DISCUSSION

The present study demonstrates the efficacy of low-dose DHEA administration on endocrine and psychoneuroendocrine parameters in early and late menopause and confirms that a low-dose DHEA supplementation increases adrenal androgens plasma levels (mainly DHEA and DHEAS) (19), which are significantly impaired during menopause.

At present, hormone therapy (HT) is the easiest way to reverse the effects of hypoestrogenism in most (if not all) the organs and tissues. In the past years DHEA has been reported to induce positive endocrine changes in both sexes, also improving the feeling of well being (6, 7, 9, 11, 14, 16, 20). Up to now most of the studies have been conducted using daily dosage of 50 mg or higher of DHEA, which resulted in inducing higher levels of some endocrine parameters (15). In fact, although daily DHEA administration of 50 mg restored the E_2 plasma levels, similarly to 100 g transdermal E_2 or 2 mg of E_2 valerate (21), this dosage determines supraphysiological levels of four androgens (A, T, 17 OHP, and dihydrotestosterone). On the contrary, the present study demonstrates that long-term treatment (12 months), using a 50% reduced daily DHEA dosage (25 mg), has similar positive hormonal effects in early and late postmenopausal women.

The significant changes of the androgenic milieu that occur during senescence are due to the reduction of 17,20 desmolase activity and this determines a progressive decrease in adrenal androgen synthesis (6, 7, 9, 15, 22), with minimal changes in F secretion as demonstrated by our data. When patients were administered the 25-mg DHEA daily dosage, both estrogens and androgens concentrations increased, similarly to what was previously reported (15), but such increases were 20%–45% lower than with the 50 mg/day therapy (18). In addition, the use of a lower DHEA dose was as effective on β-endorphin, gonadotropins, the somatotropic axis (GH–IGF-1), and on subjective symptoms as the 50-mg/d dosage (11). Interestingly, the increase in DHEAS, E_2, and T concentrations was lower and less rapid than using the 50-mg schedule (15), thus confirming that a lower dose of DHEA is enough for the metabolization/synthesis of steroids.

The efficacy of the dosage we tested is demonstrated by the fact that the E_1/E_2 ratio did not change throughout the 12 months of observation and were similar to those observed using higher doses of DHEA (15).

The increase in 17-OHP plasma levels we observed at the end of the study are not in accordance with those previously described in a shorter study (15). This might result from a different sensitivity of the 17,20 desmolase responsible for the conversion of DHEA to 17-OH pregnenolone and 17-OHP progesterone and it can be suggested that the 17,20 desmolase activity is enhanced by low doses of exogenous DHEA. However, the significantly increased P and 17-OHP concentrations with DHEA administration are responsible for the increase of allopregnanolone plasma levels, a P derivative belonging to the neurosteroid family.

During menopause and aging, significant changes take place in the central nervous system, involving glial cells and neurons, especially in terms of neuroendocrine and neurosteroid production, to induce the so-called climateric or postmenopausal symptoms, such as mood changes, anxiety, and depression (15, 19). Most of the neuroendocrine changes are due to the hypoestrogenic condition and to the reduction of neurosteroid (i.e., allopregnanolone) synthesis and concentrations (18, 23–25). Allopregnanolone (3-α-hydroxy-5-α-pregnane-20-one), the most potent endogenous anxyolitic steroid (18, 23–25), showed increasing plasma concentrations throughout the treatment interval, as previously reported (15), thus suggesting that DHEA administration positively affects psychoneuroendocrine parameters through specific neuromodulatory effects on the central nervous system (18) acting on γ-aminobutiric acid A receptors (23–25).

Low-dose DHEA administration determines also the significant increase in β-endorphin plasma levels in all subjects similarly to what was observed using higher DHEA dosages

(15). Because F is reduced and β-endorphin is increased with treatment, it can be suggested that DHEA (namely its metabolites, such as allopregnanolone and E_2) increases β-endorphin concentrations, probably increasing pro-opiomelanocortin cleavage rather than pro-opiomelanocortin synthesis. In addition F being the typical stress-induced hormone, the decrease in F levels observed throughout the study confirms that DHEA administration blunts the activity of the hypothalamic-pituitary-adrenal axis and suggests a sort of neuroprotective (antistress) role for exogenous DHEA administration.

The efficacy of long-term, low-dose DHEA administration was also evident from the significant reduction in the Kupperman score. As expected, DHEA administration was more effective on vasomotor disturbances in early postmenopausal women and on psychological disturbances in late postmenopausal women. Interestingly, DHEA supplementation did not induce changes in endometrial thickness, in agreement with previous studies (15, 26). Probably this results from the absence in the endometrial tissue of the specific enzymes responsible of the conversion from DHEA to estrogens (22) or from the apparent equilibrium between two main DHEA metabolites, E_2 and P. This effect seems comparable to that of a continuous combined estroprogestin treatment. Although no endometrial biopsy was performed in the presence of a thin endometrium at ultrasound examination, it supports the hypothesis of an atrophic evolution.

In conclusion, our data show that a daily dosage of 25 mg of DHEA restored the steroid milieu, both in early and late postmenopausal women with a lower Δ5 and Δ4 androgen increase than in previously tested dosages (15, 27) and positively affected all endocrine and neuroendocrine parameters, such as β-endorphin and neurosteroids (namely allopregnanolone), reducing postmenopausal and aging symptoms. In addition, according to our data, DHEA seems not to stimulate the endometrium. Although additional studies have to be done focusing on this last aspect, these data support and confirm that DHEA must be considered a valid compound and drug for HT in postmenopausal women and not just a "dietary supplement."

Acknowledgments: The authors are grateful to Patrizia Monteleone, M.D., Dept. of Obstetrics and Gynecology, University of Pisa, for the editorial preparation of the present manuscript.

References

1. Ibanez L, Dimartine-Nardi J, Potau N, Saenger P. Premature adrenarche —normal variant or forerunner of adult disease? Endocr Rev 2000;21: 671–96.
2. Hopper BR, Yen SSC. Circulating concentrations of dehydroepiandrosterone and dehydroepiandrosterone sulphate during puberty. J Clin Endocrinol Metab 1975;40:458–61.
3. Parker LN, Odell WD. Control of adrenal androgen secretion. Endocr Rev 1980;4:392–410.
4. Laughlin GA, Barret-Connor E. Sexual dimorphism in the influence of advancing aging on adrenal hormone levels: the Rancho Bernardo study. J Clin Endocrinol Metab 2000;85:3561–8.
5. Liu CH, Laughlin GA, Fischer UG, Yen SSC. Marked attenuation of ultradian and circadian rhythms of dehydroepiandrosterone in postmenopausal women: evidence for a reduced 17,20 desmolase enzymatic activity. J Clin Endocrinol Metab 1990;71:900–6.
6. Mortola JF, Yen SSC. The effects of oral dehydroepiandrosterone on endocrine-metabolic parameters in postmenopausal women. J Clin Endocrinol Metab 1990;71:696–704.
7. Morales AJ, Nolan JJ, Nelson JC, Yen SSC. Effects of replacement dose of dehydroepiandrosterone in men and women of advancing age. J Clin Endocrinol Metab 1994;78:1360–7.
8. Berr C, Lafont S, Debuire B, Dartignes JF, Baulieu EE. Relationships of dehydroepiandrosterone sulphate in elderly with functional, physiological, mental status and short term motality: a French community-based stady. Proc Natl Acad Sci USA 1996;93:13410–5.
9. Stomati M, Rubino S, Spinetti A, Parrini D, Luisi S, Casarosa E, et al. Endocrine, neuroendocrine and behavioural effects of oral dehydroepiandrosterone sulfate supplementation in postmenopausal women. Gynecol Endocrinol 1999;13:15–25.
10. Flynn MA, Weaver-Osterholtz D, Sharpe-Timms KL, Allen S, Krause G. Dehydroepiandrosterone replacement in aging humans. J Clin Endocrinol Metab 1999;84:1527–33.
11. Genazzani AD, Stomati M, Strucchi C, Puccetti S, Luisi S, Genazzani AR. Oral dehydroepiandrosterone supplementation modulates spontaneous and growth hormone-releasing hormone-induced growth hormone and insulin-like growth factor-1 secretion in early and late postmenopausal women. Fertil Steril 2001;76:241–8.
12. Phillips GB. Relationship between serum dehydroepiandrosterone sulfate, androstenedione, and sex hormones in men and women. Eur J Endocrinol 1996;134:201–6.
13. Guazzo EP, Kirkpatrick PJ, Goodhyer IM, Shiers HM, Herbert J. Cortisol, dehydroepiandrosterone (DHEA), and DHEA sulfate in the cerebrospinal fluid of man: relation to blood levels and the effect of age. J Clin Endocrinol Metab 1996;81:3951–60.
14. Johannsson G, Burman P, Wiren L, Engstrom BE, Nilsson AG, Ottosson M, et al. Low dose dehydroepiandrosterone affects behavior in hypopituitary androgen-deficient women: a placebo-controlled trial. J Clin Endocrinol Metab 2002;87:2046–52.
15. Stomati M, Monteleone P, Casarosa E, Quirici B, Puccetti S, Bernardi F, et al. Six-month oral dehydroepiandrosterone supplementation in early and late postmenopause. Gynecol Endocrinol 2000;14:342–63.
16. Genazzani AR, Petraglia F, Bernardi F, Casarosa E, Salvestroni C, Tonetti A, et al. Circulating levels of allopregnanolone in humans: gender, age and endocrine influences. J Clin Endocrinol Metab 1998; 83:1–5.
17. Daughaday WH, Mariz IK, Blethen SL. Inhibition of access of bound somatomedin to membrane receptor and immunobinding sites—a comparison of radioreceptor and radioimmunoassay of somatomedin in native and acid-ethanol extracted serum. J Clin Endocrinol Metab 1980;51:781–5.
18. Stomati M, Bersi C, Rubino S, Palumbo M, Comitini G, Genazzani AD, et al. Neuroendocrine effects of different oestradiol-progestin regimens in postmenopausal women. Maturitas 1997;28:127–35.
19. Stomati M, Casarosa E, Bernardi F, Tonetti A, Genazzani AD, Luisi M, Genazzani AR. DHEA and andropause. In: Genazzani AR, Artini PG, D'Ambrogio G, Gadducci A, Gambacciani M, Genazzani AD, eds. Diagnostic procedure and latest development in gynecologic and obstetric investigation. CIC Edizioni Internazionali: Rome, Italy, 2001: 102–10.
20. Wolf OT, Neumenn O, Helhammer DH, Geiben AC, Strasburger CJ, Dressendorfer RA, et al. Effects of a two-week physiological dehydroepiandrosterone substitution on cognitive performance and well-being in healthy elderly women and men. J Clin Endocrinol Metab 1997;82: 2363–7.
21. Kuhl H. Pharmacokinetics of oestrogens and progestogens. Maturitas 1990;12:171–97.
22. Arlt W, Justl HG, Callies F, Reincke M, Hubler D, Orttel M, et al. Oral dehydroepiandrosterone for adrenal androgen replacement: pharmacokinetics and peripheral conversion to androgens and estrogens in young healthy females after dexamethasone suppression. J Clin Endocrinol Metab 1998;83:1928–34.
23. Paul SM, Purdy RH. Neuroactive steroids. FASEB J 1992;6:2311–22.
24. Mellon SH, Deschepper CF. Neurosteroid biosynthesis: genes for adrenal steroidogenic enzymes are expressed in the brain. Brain Res 1993;629:283–92.
25. Robel P, Baulieu EE. Neurosteroids: biosynthesis and function. Trends Endocrinol Metab 1994;5:1–8.
26. Labrie F, Belanger A, Van LT, Labrie C, Simard J, Cusan L, et al. DHEA and the intracrine formation of androgens and estrogens in peripheral target tissues: its role during aging. Steroids 1998;63:322–8.
27. Yen SSC, Morales AJ, Khorram O. Replacement of DHEA in ageing men and women: potential remedial effects. Ann NY Acad Sci 1995; 774:128–42.