DHEA: a natural steroid for the treatment of menopausal women

A.D. GENAZZANI¹, A. PRATI¹, S. SANTAGNI¹, E. RATTIGHIERI¹, E. CHIERCHIA¹, G. MARINI¹, G. DESPINI¹, A.R. GENAZZANI²


DHEA is one of the main adrenal hormones that progressively reduces its plasmatic levels starting from the 30ies. This phenomenon implies not only the reduction of the plasmatic androgens, but also the decrease of a peculiar class of hormones, named neurosteroids, in particular allopregnanolone, the most powerful one, characterized by antidepressant and ansiolitic effect.

During the latest years the putative role of the use of DHEA as replacement therapy for menopausal women has been under consideration, especially because of the failure of hormonal replacement therapy (HRT) in improving some discomforts of menopausal age, such as loss of libido and changes of mood.

This review aims to elucidate the peculiar aspects of DHEA administration and its putative use as substitutive/integrative hormonal treatment alone or in combination with the traditional HRT.

KEY WORDS: Menopause - Hormone replacement therapy - DHEA - Neurosteroids - Allopregnanolone - Libido - Mood - Climateric symptoms.

Menopausa - Terapia ormonale sostitutiva - DHEA - Neurosteroidi - Allopregnanolone - Libido - Umore - Sintomi climaterici.

Introduction

The possible use of DHEA (dehydroepiandrosterone) as alternative treatment to the traditional hormonal replacement therapy (HRT) has been discussed for a long time. This hypothesis is supported by the fact that this neurosteroid is metabolized to several steroid hormones, that decrease their plasma levels progressively during menopausal transition. The aim of this review is to give insights about the peculiar aspects of DHEA administration and its putative use as substitutive/integrative hormonal treatment both alone or in combination with the traditional hormonal replacement therapy. The aim is to discuss whether DHEA could become a useful completion to HRT to be started from perimenopausal age, considering that the adrenal pro-
DHEA: a natural steroid for the treatment of menopausal women

The adrenal DHEA and its sulfate ester dehydroepiandrosterone sulfate (DHEAS) are produced all along life in both sexes (1). They occur in high blood levels in young adults and decrease with advancing age (2, 3). This event, called aging, is a physiologic change that starts around the 3rd decade in human race, and it is triggered by the activation of an hypothetical hypothalamic pacemaker and/or other neurologic areas located in the cerebral cortex. Aging influences cerebral and pituitary functions, inducing changes and several endocrine adaptations such as the decrease of GH levels inducing a lower hepatic production of IGF-1, the increase of LH and FSH levels triggered by a lower synthesis of estradiol and testosterone from ovaries, the decrease in ACTH levels limiting the adrenal DHEA production.

Together with the progressive reduction of DHEA/S plasma levels, we observe a constant and progressive increase in cortisol levels during years. This lead to a mild grade of hypocortisolism typical of elderly, which constitutes a biological safety mechanism on one side, but it is also a trigger for metabolic and neurological imbalance: steadily high cortisol levels could lead to neurotoxicity and hyperglycemia.

Dehydroepiandrosterone and its sulfate ester are neurosteroids, that can be synthesized by neurons and glial cells, increasing the effects of glutamate, an excitatory neurotransmitter (4), and decreasing the effects of GABA, an inhibitory neurotransmitter (5). DHEA could also act as neuroprotective agent (6, 7), modulating also the immune system (8): there are clinical and experimental evidences that DHEA administration induces the activity of natural killer cells (8) and might be effective in the treatment of immunological disease (9, 10). Both the immunological and neural effects of DHEA/S may be related to its powerful antiglucocorticoid action (7, 11), counteracting the negative effects of cortisol. Therefore lower DHEA blood levels in elderly make body more vulnerable to the negative effects of cortisol (12) in term of neurotoxicity and abnormal metabolic functions.

Aging starts around 30-35 years in both sexes but it is the occurrence of the hypoestrogenism of menopause, typically characterized by the decay of ovarian function that worsen the biological features in women: the combination of aging and low estrogen blood levels lead to changes in many organs and tissues.

Since DHEA/S levels decrease with age, it has been postulated that various age-associated changes might be preventable by DHEA supplementation (1). A community-based cohort study, in 940 participants followed for 27 years, indicated that DHEA/S level may be a predictor of longevity in men, independently from age, blood pressure and plasma glucose (13). Other epidemiological evidences suggest that the DHEA/S concentrations are independently and inversely related to death from any cause and death from cardiovascular disease in men over age 50 (14). In addition some studies showed that patients diagnosed with dementia (15-18) have lower than normal levels of DHEA/S in the serum, while others reported no difference (19, 20). A prospective observational study of 394 women aged 65 and over followed for four to six years, showed no relation between serum DHEA levels and cognitive performance (21), while in a cross-sectional study of 295 women, aged 21-77 years, higher endogenous DHEA levels were independently and favourably associated with better executive function, concentration and working memory (22).

DHEA supplementation

The use of DHEA as integrative treatment in postmenopausal women induces the increase of DHEA, DHEAS, androstenedione, testosterone, dihydrotestosterone, estradiol, progesterone, β-endorfin, allopregnanolone plasma level and the decrease of cortisol (23). DHEA has a precise metabolic pathway and must be considered a sort of reservoir of all steroid hormones. Indeed in the central nervous system DHEA is converted in testosterone thanks to the actions of two enzymes, 3β-OH dehydrogenase and 17β-hydroxysteroid oxidoreductase, and then in estradiol thanks to the aromatase, ubiquitarious in the brain (24). So, at this level, there are enzymes able to transform DHEA in estrogens, being androgens the intermediate products of this pathway, having specific effect on cerebral level: effectively they improve synaptic plasticity, cellular differentiation and proliferation, neurotransmitter system biosynthesis and function, genic expression and apoptosis (25). The improvement of all these complex mechanisms support the integrity of cognitive functions, with no changes in mood, no loss of libido and sexual desire, arousal and excitability, also in postmenopausal women (25) (Figure 1). Although a 2009 Cochrane review (1) states that DHEA supplementation induces few healthy effects, mostly induced by individual fac-
tors, such as age, gender, emotional state with no improvement of cognitive function, a decay was evident in the placebo treated group (26). However it is relevant to point out that only five studies were considered and only two studies had the observation interval of at least one year (1).

Morgan et al. studied DHEA plasma level in depressed and asymptomatic postmenopausal women, showing that DHEA levels were lower in depressed patients (27) and that DHEA administration induced the increase not only of DHEA level, but also of all others steroids derived from DHEA, such as progesterone, androstenedione, tetrahydroprogesterone, i.e. allopregnanolone (27) (Figure 2).

To our knowledge, a normal sexual function needs not only adequate levels of estrogens, progesterone and androgens, so that to modulate both CNS and genital tissues, but also of catecolamin, (i.e. epinephrine and norepinephrine), prolactin, oxytocin and β-endorphin (28). Many studies confirm that DHEA treatment determines an increase in androgens plasma levels (Δ4 and Δ5 androgens), improving sexual function better than estroprogestin therapy or tibolone, thus supporting the hypothesis that estrogens are modulators of sexual function in women (29). Moreover DHEA is a neurosteroid acting directly as a modulator of receptor of various neurotransmitter, such as GABA, N-metil-D-aspartate, and of sigma-1 receptor (29), all implicated in the control of sexual function.

It is well known that the menopausal hypoandrogenism is at the basis of the loss of libido, typical of physiological or surgical menopause, determining a real disease called hypoactive sexual desire disorder (HSDD), characterized by the lack or absence of sexual fantasies and desire for sexual activity, in combination with marked distress or interpersonal difficulties, very common especially after ooforectomy (30). In this case it is necessary to correct the androgens and estrogens deficiency, to improve and positively affect the sexual function and mood, but also psychotherapy plays a crucial role when a personal or interpersonal discomfort is evident. A recent study suggests transdermal testosterone at the dose of 300 µg/day as a possible therapy, in combination or not with an estroprogestin treatment, both in physiological and surgical menopause, without any relevant side effects (30).

Since androgens play a relevant role also in women because of their influence on behavioral effects, mood, libido and sexual function in general, the possible use of DHEA to correct menopausal hypoandrogenism has been considered more natural and better tolerated than others hormonal treatments.

DHEA has been known and used for years because its preventive effects on accumulation of abdominal fat and positive modulation on insulin resistance in overeating rats (31), that was confirmed also in man (8): it was observed that DHEA induced a significant decrease in both visceral and subcutaneous fat in elderly men and women and a reduction of the area under insulin curve during oral glucose tolerance test (OGTT). Indeed DHEA supplementation resulted in a significant improvement in insulin action that correlated with the...
DHEA: a natural steroid for the treatment of menopausal women

reduction in visceral fat, so these findings provide evidence that DHEA replacement may partially reverse the aging-related accumulation of abdominal fat in elderly people. It has been supposed that long-term DHEA replacement therapy might protect against development of the metabolic/insulin resistance syndrome (32). Others studies demonstrated that DHEA may be beneficial for cardiovascular health, but the mechanisms of such DHEA action are unclear (33). Indeed in vitro, DHEA increased endothelial cells (EC) expression of endothelial nitric oxide synthase and activity of extracellular signal-regulated kinase 1/2. In vivo, DHEA increases flow mediated dilation and laser Doppler velocimetry and reduces total plasma cholesterol. Thus, DHEA increases EC proliferation in vitro by mechanism(s) independently of either androgen receptor or estrogen receptor and in vivo enhances large and small vessel EC function in postmenopausal women (33).

Beneficial effects of DHEA supplementation are similar to those of hormonal replacement therapy, but the benefits on mood and depressed attitude typical of menopausal age are higher, similarly to psychosexual well-being and sexual desire. Moreover DHEA administration exerts a protective action on bone since prevents osteopenia/osteoporosis: indeed Weiss et al. (34) reported that DHEA supplementation in postmenopausal women increases bone mass if calcium and vitamin D are present in the diet, thus supporting the concept that DHEA is an option to act on bone health, without any side effects.

Concerning climacteric symptoms, women treated with DHEA (at the dose of 10 mg/day), HRT or tibolone had the similar improvement of climacteric symptoms (29).

Evidence from controlled trials on side effects of DHEA is inconsistent: in the last years many studies evaluated the use of DHEA also at doses higher than 10 mg/day without relevant side effects (1). Although the large diffusion of the use of DHEA in the US, where it is considered as integrative treatment, no relevant study has been performed, though worldwide literature has reported of billion of subjects undergoing to this treatment without serious side effects. Moreover Food and Drug Administration (FDA) never reported adverse events, demonstrating the safety of DHEA, as expected. To our knowledge and experience, DHEA could represent a good and safe hormonal replacement therapy, similar to HRT being effective on climacteric symptoms (35).
Endocrine effects of DHEA supplementation

Beneficial effects of DHEA treatment are similar to those induced by tibolone or HRT. In fact all treatments improve hormonal milieu and neurosteroid plasma levels and this can be observed during DHEA supplementation alone as well as in combination with HRT in postmenopausal women.

Let’s discuss some of the main changes:

DHEA/S: DHEA treatment increases DHEA and DHEAS plasma levels, while hormonal replacement therapy does not improve their synthesis. In fact DHEA levels showed a decline during HRT administration, at least after the 3rd month of follow-up: the percentage change in DHEA levels during follow-up was independent from the type of HRT or progestin used or between the transdermal and oral administration (36). Indeed DHEA serum levels increase only during DHEA treatment alone or in combination with HRT. Recently Pluchino et al. demonstrated such concept since they reported that in patients treated with DHEA, DHEA serum levels increased progressively during the entire treatment interval with a significant rise starting from the 3rd month for women aged about 53 and from the 6th month for women aged 57 (37). Baseline DHEA levels were higher in younger women, but similar levels were observed in both groups after 6 months of therapy (37). Probably this difference between the two groups was due to a slow but necessary reinduction of cellular enzymes assigned to DHEA metabolization (Figure 3).

Testosterone, dihydrotestosterone, androstenedione: since traditional HRT does not increase androgens plasma levels but, on the contrary, could decrease them furthermore, this is probably the reason why HRT fails to improve several aspects of female sexuality which are induced by the menopause-related androgen deficiency. It is relevant to mention that various studies reiterate the need to combine HRT with androgens, such as DHEA or transdermal testosterone to positively affect female sexuality (37). This is extremely important in...
patients going towards surgical menopause in which hypoandrogenism has a marked and pronounced progression.

The same study demonstrated that testosterone levels increased progressively from the 1st month of treatment in patients receiving only DHEA and after the 3rd month in DHEA-HRT treated group (37). Interestingly, delta4-androstenedione levels increased slowly and progressively in both groups, with a significant rise after the 3rd month in DHEA-treated women and after the 6th month in DHEA-HRT treated ones (37).

Estrogens: estrogens plasma levels increase during HRT treatment; indeed estradiol levels show a progressive marked increase during follow-up, being highly significant already after 1 month of treatment (36). The percentage change in estradiol levels during follow-up is not significantly different among the different estrogen-progestin therapy groups independently from the presence or the type of progestin used or between the transdermal and oral estradiol administration (36). It is relevant to observe that also DHEA treatment alone increases estradiol plasma level (37). Pluchino et al. demonstrated that patients receiving both DHEA and HRT showed higher levels of estrone (E1) and estradiol (E2) in comparison to those receiving DHEA alone, but very similar to those receiving HRT alone (37). In DHEA or DHEA-HRT treated patients, estradiol plasma levels showed a significant increase in all groups starting from the 3rd month if the supplementation starts within 3 years from the beginning of menopause, allowing the achievement of high estradiol levels (37).

Despite the elevated estrogen plasma levels reached with the combination of both therapies, leading to plasma concentration higher than 50 pg/ml, they are apparently no significant changes in the endometrium thickness, in any age groups (38). These data are in accordance with previous studies, showing no effects of DHEA (independently from the route of administration in cream or orally) on the endometrium (39, 40), probably because of the absence of the required enzymes for the transformation of DHEA into estradiol at this level. However it cannot be excluded that the lack of any effect on the endometrium might be due to a sort of balanced effect(s) between both DHEA-derived estradiol and progesterone. Estrogen effects on the other targets are clearly evident and their central modulation is demonstrated by the significant decrease of gonadotropins during the treatment (38). Moreover Panjari et al. study demonstrated the safety of one-year therapy with 50 mg/day DHEA on the endometrium too (41).

Progesterone: progesterone levels showed a significant increase during DHEA treatment alone or in combination with HRT, as well as under HRT alone in post-menopausal women (29, 37). Other studies showed that progesterone levels remained constant in all different aged groups of patients under DHEA treatment (38). Recently it has been showed that in women undergoing to a daily dosage of 10 mg of DHEA the increase of progesterone and 17-hydroxyprogesterone levels occurred after the 6th month of treatment, while in patients treated with tibolone no change in progesterone and 17-hydroxyprogesterone levels occurred during the entire treatment period (29). It is well known that progesterone levels significantly increases during different HRT administration, with a rapid and marked increase after 1 month, reaching at the 3rd months (36). The percentage change in progesterone levels during the treatments is relatively different among the groups: in particular, when patients used HRT with a 19-nor derivative progestin we do not observe a significant increase in progesterone levels, reaching statistical significance at 6-month follow-up (36).

Allopregnanolone: allopregnanolone is the most important neurosteroid and its level significantly increases during HRT, with a progressive increase during the treatment with higher and stable levels after 2-3 months of treatment. This is the most powerful endogenous neurosteroid, with an antidepressant and anxiolytic effect. When transdermal estradiol is administrated a significantly higher percentage change in allopregnanolone levels than the orally treated group was observed, starting from the 3rd month (36). The highest increase is obtained in patients receiving HRT with progesterone molecules different from 19-nor derivatives (like NETA or LNG, which are not transformed into progesterone and consequently into allopregnanolone) (36). Allopregnanolone levels show a progressive increase starting from the 6th month during the 10 mg/day DHEA treatment alone (37), as well as during the tibolone and standard HRT treatment (29). It is interesting to underline that allopregnanolone increase is higher if all hormonal therapies are started within 12-18 months from the beginning of menopause: indeed also the combination of DHEA with HRT, if started in late menopause, did not induce adequate increase of allopregnanolone levels (37). This suggests that the addition to an estrogen-progestin treatment cannot further modulate the biosynthetic activity of the adrenal gland, which is the main source of circulating allopregnanolone in postmenopausal women (37). This supports the fact that aging negatively affects adrenal DHEA.
synthesis/release as well as the response of adrenal steroidogenesis to hormonal treatment, evidencing the importance of timing for HRT and/or DHEA therapy to reverse adrenal ageing and to obtain the most positive hormonal results (37).

Estrogens per se are able to increase allopregnanolone levels because they act directly on the enzymes involved in the biosynthetic pathway of allopregnanolone formation; nevertheless, when a progesterin molecule, which may be converted to progesterone, is added, a further increase of allopregnanolone occurs (36) (Figure 4).

Cortisol: DHEA and/or HRT are able to induce a decrease in cortisol levels. If HRT contains oral estrogens in combination with NETA no change in cortisol level were observed, conversely a decrease occurs with transdermal estradiol (36) and this reduction of cortisol levels is higher than what observed under oral HRT (36). Cortisol levels show a more rapid reduction if the hormonal therapies (whatever the compounds are used) are started at the beginning of the menopause and the lower cortisol levels is observed in subjects under DHEA administration (37).

Beta-endorphin: a higher response of beta-endorphin occurs under HRT than under DHEA treatment alone, especially when starting hormonal treatments in early menopause (37). This might be related to the higher increase of circulating estrogens (E1 and E2) due to HRT, since central and peripheral contents of this opioid are strictly dependant on the estrogen level (37), but aging process might negatively affect the estrogen modulation of synthesis/release of this opioid, so on such basis it is evident that hormonal therapies have to be started as soon as possible (37).

Stomati et al. investigated the effects of a 6-months treatment with 50 mg/day DHEA on the adrenal function, evaluating the product/precursor ratio of adrenal steroid levels before and after the treatment, to assess the relative activities of the adrenal cortex enzymes (38): at the 6th month the 17,20-desmolase, sulfatase and/or sulfotransferase, 17-20-lyase and 5α-reductase activities significantly increased, while the 3β-hydroxysteroid-oxidoreductase activity did not vary. On the contrary, the 11-hydroxylase and/or 21-hydroxylase activities showed a significant decrease after 6 months of treatment (38). The sensitivity of the adrenal gland to dexamethasone suppression increased after 3 and 6 months of treatment in terms of DHEA, DHEAS and allopregnanolone, while it remained unchanged for cortisol, 17-OHpregnenolone, androstenedione, progesterone, 17-OH progesterone (38). These data support the hypothesis that DHEA administration clearly positively modulates adrenal gland enzymatic pathways. Other studies demonstrated that even at low DHEA dosage, as low as 10 mg/day, the adrenal synthesis of Δ-4 and Δ-5 androgens is enhanced, since DHEA/S levels continued to increase all long the treatment interval (37).
DHEA: a natural steroid for the treatment of menopausal women

HRT, DHEA or both?

Hormonal replacement therapy is able to influence positively neurosteroids levels in postmenopausal women, but it does not induce any change in the androgenic milieu, which is very important for the women well-being: that is why it was relevant to find new therapeutic strategies that could face this problem, such as transdermic testosterone, vaginal testosterone or DHEA and oral DHEA treatment.

Moreover, experimental evidence suggests that DHEA and DHEAS antagonize GABAergic activity, producing an increase in CNS neuronal excitability, while allopregnanolone acts as a GABAA receptor agonist, with strong anxiolytic effects (38). It is possible to speculate that the beneficial effects of DHEA supplementation on sense of well-being, cognitive functions, mood and behavior may be determined by this steroid’s direct action on the CNS; these effects may also be mediated by active metabolites of DHEA or through its relevant effects on the synthesis of allopregnanolone (38). Also the significant decrease in cortisol synthesis and release throughout DHEA supplementation may positively influence the organism’s response to stress, since cortisol has been described as a CNS neurotoxic molecule (38).

Bernardi et al. demonstrated that HRT, though beneficials on several organs, induces a relative ovarian and adrenal androgen deficiency, with a parallel decrease of DHEA and cortisol secretion (with the exception of tibolone). This clearly supports the idea of the use of whatever type of HRT in combination with a low dose DHEA therapy, that may be helpful to antagonize HRT bad impact on adrenal function (in particular on enzymatic expression) and positively influence the general response to stress.

Controversial results has been reported about the ideal dose of DHEA therapy to be used for postmenopausal women, but to our knowledge probably the best one is 10-20 mg/day of DHEA if administrated alone or 10 mg/day if in addition to a conventional estrogen replacement regimen, in order to assess the DHEA impact on estrogenic, progestogenic, glucocorticoid and androgenic milieu respect to standard HRT (29, 37).

It has been proposed also DHEA as transdermal treatment. Such route was able to restore optimal circulating DHEA plasma levels, while vaginal administration leads to a lower increase of DHEA plasma levels, with similar beneficial effects resulting in good circulating estrogens levels. Labrie et al. (42) demonstrated that a vaginal daily low-dose DHEA therapy solves vaginal atrophy signs and symptoms and provides a significant improvement in sexual function, with minimal changes in circulating hormonal milieu (42). Only one study by Labrie et al. reported that vaginal daily DHEA treatment enhances arousal, desire and lubrication in healthy postmenopausal women, evaluated using the Abbreviated Sexual Function (ASFQ) questionnaires (43).

Since various routes of DHEA administration (oral, transdermal and vaginal) exist, and being DHEA a more natural compound than HRT, DHEA might be a more interesting treatment for those physicians and gynecologists concerned by the fear of cancer.

The main purpose of the hormonal replacement therapy is to provide a solution to the estrogens deficiency caused by the progressive decline of ovarian function, being this cause of functional alterations of CNS, muscle-skeletal system, female genital system, skin, cardiovascular system, metabolism. The combination of HRT with DHEA has been thought to be useful to maintain adequate Δ-4 and Δ-5 androgens levels, essential for women well-being too, especially for the important central regulation on mood and sexual desire. This hypothesis of the combination of HRT with DHEA is based on the fact that they have both necessary and complementary effects and that DHEA counteracts the HRT induced hypoandrogenism. The combination between these two therapies should be started during the perimenopausal period, when it could be initially chosen a cyclic sequential therapy, that could be later changed in a continuous combined one and then continuing with DHEA alone or in combination with a low dose HRT. The ideal dosage for such supplementation is probably 10 mg/day.

DHEA administration restores not only estradiol, but also androgens beneficial effects, differently from HRT alone. This is probably the reason why HRT fails to improve some aspects of mood and female sexual function which are associated to the menopause-related androgen deficiency, such as loss of libido and/or sexual desire, arousal and excitability. Pluchino et al. demonstrated that 10 mg/day of DHEA was able to increase plasma androgen levels, whereas the estrogen-progestin therapy alone did not, to enhance plasma level of estrone, estradiol, progesterone, to positively modify adrenal synthesis of cortisol (reduction) and allopregnanolone (increase) and to increase plasma concentration of beta-endorphin (37).

In addition Genazzani et al. reported that symptomatic early postmenopausal women, receiving 1-year oral DHEA therapy at a daily dose of 10 mg, improved their climacteric symptoms similarly to HRT or ti-
bolone (29); interestingly, using the McCoy Questionnaire, although the effect on sexual function is similar for dHeA and HrT, estroprogestin treatment induced higher values of circulating estradiol than DHEA, supporting the hypothesis that estrogens are not the only mediators of sexual function in women (29). It is evident the relevance of a very low dose like 10 mg/day of DHEA, in combination with HrT, starting from the perimenopausal period or eventually after a period of conventional HRT or after oral contraceptive treatment.

In this contest DHEA supplementation may represent a strategic therapy for postmenopausal women in addition to HRT, so that to correct the decrease in androgens levels peculiar of aging, but also caused by HRT induced decrease of adrenal function: this event might be avoided thanks to the combination of HRT with DHEA. Aging seems to negatively affect adrenal DHEA synthesis as well as the response of adrenal steroidogenesis to hormonal treatments, evidencing the importance of timing for HRT or DHEA therapy to reverse and for counteract adrenal ageing and to obtain the best response to hormonal treatment, in terms of androgen milieu and in a more adequate adrenal function (37).

Since in literature serious DHEA side effects have never reported and considering that the Food and Drug Administration (FDA) has never observed adverse events after DHEA administration, DHEA seems to be a putative optimal natural hormonal treatment. Though considering the absence in the endometrium of the required enzymes for the transformation of DHEA into estradiol, additional studies, on larger population, are needed to evaluate in efficacy and safety long term effects of DHEA in combination with HRT.

Nevertheless, the decision to start whatever hormonal replacement therapy should be taken after a global clinic and anamnestic evaluation of the postmenopausal patient. Furthermore the choice of the type of therapy should be strictly personalized on the basis of patients characteristics and necessities. The treatment needs always an informed consent by the patient and it remains clear that a specific regular follow-up is always needed when in presence of long term treatment.

In conclusion DHEA might be proposed as a putative treatment both alone or in combination with HRT, for all of those peri- or postmenopausal women who are considered optimal for hormonal replacement treatment.

References

10. Van vollenhoven RF, Engleman EG, McGuire JL. An open study of dehydroepiandrosterone in systemic lupus erythemato-

A.D. Genazzani et al.
DHEA: a natural steroid for the treatment of menopausal women


