

DHEA after Menopause

Sole Source of Sex Steroids and Potential Sex Steroid Deficiency Treatment

Fernand Labrie, MD, PhD

Following complete cessation of estrogen secretion by the ovaries at menopause, all estrogens and all androgens come from dehydroepiandrosterone (DHEA) of adrenal origin. While being an inactive molecule by itself, DHEA is transformed at various levels and ratios into estrogens and/or androgens only in the tissues that possess the required cell-specific steroidogenic enzymes with minimal or no release of the active hormones in the blood. In fact, following their synthesis, the estrogens and androgens are inactivated at their intracellular site of formation before being released in the blood as water-soluble metabolites. This process, called intracrinology, is unique to the human species and protects the tissues, such as the endometrium, which should not normally be exposed to estrogens or androgens after menopause.

Despite its essential characteristic of tissue specificity, one problem with DHEA is that from the maximal values found at the age of 30, its serum levels are already decreased by an average of 60% at the time of menopause. Moreover, serum DHEA levels are highly variable, going from negligible values in some women to 9-10 ng/mL in others. The low circulating DHEA levels are accompanied by a

parallel fall in the total pool of androgens and estrogens.

A very compelling demonstration of the efficacy and safety of DHEA has recently been obtained in a pivotal Phase 3, placebo-controlled, randomized clinical trial in which postmenopausal women suffering from vaginal atrophy received daily DHEA or placebo intravaginally for 3 months. A rapid and very marked improvement of all the symptoms and signs of vaginal atrophy was observed, with no change in circulating estradiol or testosterone. An additional benefit not seen with estrogens was the finding of a significant improvement of all domains of sexual dysfunction, namely desire, arousal, orgasm and pleasure. As expected from physiologic amounts of DHEA administered intravaginally to women deficient in DHEA, no negative side effect has been observed. This is in agreement with the belief that the women receiving a low dose of DHEA (6.5 mg) should not be different, hormonally speaking, from the group of postmenopausal women who have sufficient endogenous DHEA to remain free of the symptoms of menopause. While exceptional efficacy and medical value has just been demonstrated for vaginal atrophy, a series of other clinical data suggests that DHEA could also exert beneficial effects on bone and muscle loss, skin atrophy, adiposity and type 2 diabetes, all of which are related to sex steroid deficiency after menopause.

DHEA after Menopause: What the Research Reveals about Intracrinology

The traditional concept of sex steroid physiology in women is based on the assumption that all estrogens were of ovarian origin and that androgens are only present in minute amounts. The relatively recent development of mass spectrometry technology has permitted us to gain new and crucial information in this field.¹⁻³ In fact, the traditional concept does not apply to humans and is valid only for animal species lower than primates, in which the ovaries are the only source of sex steroids. This concept was derived from the erroneous belief that serum estradiol (E_2) was the valid estimate of total estrogen exposure in women, thus leading to the incorrect assumption that estrogens were limited to premenopause based upon the observation that serum E_2 decreased to very low levels at menopause. In reality, however, the presence of important concentrations of E_2 in the general circulation is limited to premenopause when, the ovaries secrete estrogens in large amounts in the circulation. During these premenopausal years, ovarian E_2 secretion is finely regulated by a negative feedback control system involving the brain (mainly the hypothalamus) and the anterior pituitary gland (Figure 1). This feedback mechanism adjusts ovarian E_2 secretion to the different phases of the menstrual cycle and permits normal fertility, pregnancy and lactation.

Contrary to the impression given by the serum levels of E_2 , the ovary is not the only source of sex steroids. In fact, sex steroid formation does not cease at menopause; it does, however, become exclusively tissue-specific and depends upon DHEA availability.

Humans, along with other primates, are unique among animal species in having adrenals that secrete large amounts of the inactive precursor steroid DHEA, which is converted into active androgens and/or estrogens in specific peripheral tissues (Figure 1).⁴⁻⁶ After cholesterol, DHEA is the most abundant steroid in the human blood. This precursor steroid is transported by the general circulation to the target tissues, where it is transformed into active sex steroids by the process known as intracrinology.⁷ In fact, DHEA is an essential precursor or intermediate for the formation of all natural androgens and estrogens in humans.

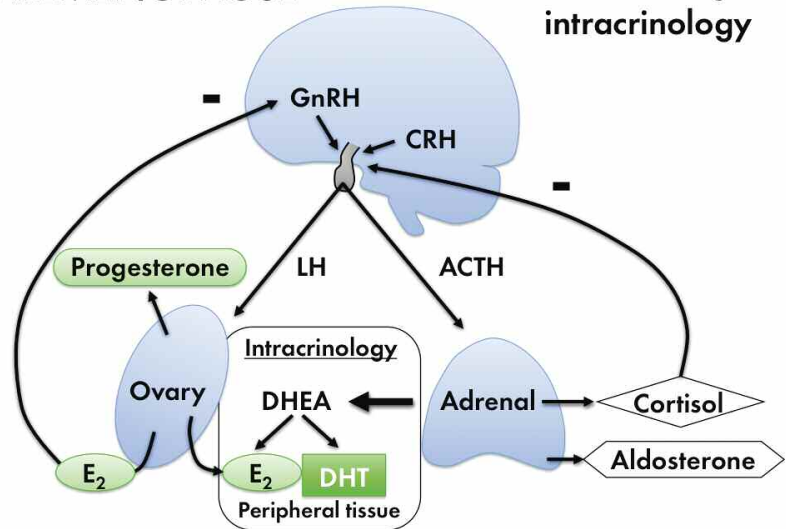
At menopause, since the ovary stops making estrogens, DHEA of adrenal origin becomes the exclusive source of estrogens (Figures 2 and 3). Since, according to normal physiology, women are no longer exposed to systemic estrogens after menopause, it is reasonable to believe that the nonphysiologic situation created by the administration of estrogens could be responsible for at least some of the side effects reported by women receiving traditional estrogen therapy (ET) and estrogen/progestin (hormone therapy [HT]).⁸⁻¹⁵ These side effects are in addition to the well-recognized stimulation of the endometrium by unopposed estrogens, and the resulting hyperplasia and risk of carcinoma.

Mechanism of Action

DHEA, the exclusive source of sex steroids after menopause, provides estrogens and/or androgens only to the tissues that possess the required enzymes to transform DHEA. Major

PREMENOPAUSE

New findings:
intracrinology



KEY: ACTH = adrenocorticotropic hormone; CRH = corticotropin releasing hormone; DHT = dihydrotestosterone; E_2 = estradiol; LH = luteinizing hormone; GnRH = gonadotropin-releasing hormone

Figure 1. Schematic representation of the combined ovarian and adrenal sources of estrogens in premenopausal women. In addition to estrogens secreted by the ovary, DHEA, an inactive prehormone secreted by the adrenal glands, is converted in specific target tissues into androgens and/or estrogens via the process of intracrinology. Only very small amounts of these peripherally made sex steroids diffuse into the circulation since they are inactivated in the same cells in which their formation and action takes place before being released as inactive conjugated metabolites in the blood.

progress in this area has been made by the elucidation of the structure of most of the tissue-specific genes that encode the steroidogenic enzymes responsible for the transformation of DHEA into androgens and/or estrogens locally in peripheral tissues.¹⁶⁻²¹ This transformation of DHEA is, however, exerted at different levels and at specific ratios of estrogens and androgens, depending upon the cell type, with no transformation in the human uterus. In addition, it is important to note that the active hormones are inactivated at their site of synthesis before being released outside the cells, thus explaining why there is minimal or no leakage of the active sex steroids into the circulation. A most convincing example of the intracrine, or strictly local, action of DHEA is pro-

vided by the highly beneficial and rapid effects observed on vaginal atrophy²²⁻²⁴ following intravaginal administration of DHEA, an effect that is observed with no significant change in circulating estrogens or androgens.^{25,26}

This novel strategy has recently been commented upon in a 2009 editorial by Simon.²⁷ "Other new and unique approaches include developing 'formed-in-place' estrogens and androgens, in which precursor compounds (ie, dehydroepiandrosterone) are provided vaginally only to be converted to estrogens and androgens intracellularly (locally), so that only the vaginal epithelium actually 'sees' the estrogen, recalling that the normal endometrium does not contain aromatase." (Source: Endoceutics

(continued on page 19)

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(continued from page 15)

Inc, Quebec, Canada.)

Changes over Time and High Variability

The secretion of DHEA markedly decreases with age, with an average loss of 60% already observed at time of menopause^{1,5,28,29}(Figure 4). This marked reduction in the secretion of DHEA by the adrenals during aging²⁹ results in a parallel fall in the formation of androgens and estrogens in peripheral target tissues, a situation believed to be associated with a series of medical problems of menopause: insulin resistance,³⁰ fat accumulation,³¹ bone loss, muscle loss, type 2 diabetes, vaginal atrophy and skin atrophy,^{5,27,32-34} memory and cognition loss,¹⁵ and possibly Alzheimer's disease.

In addition to markedly decreasing with age, the serum levels of DHEA are highly variable, with some women having barely detectable serum concentrations and others demonstrating values of up to 9-10 ng/mL¹ (Figure 5).

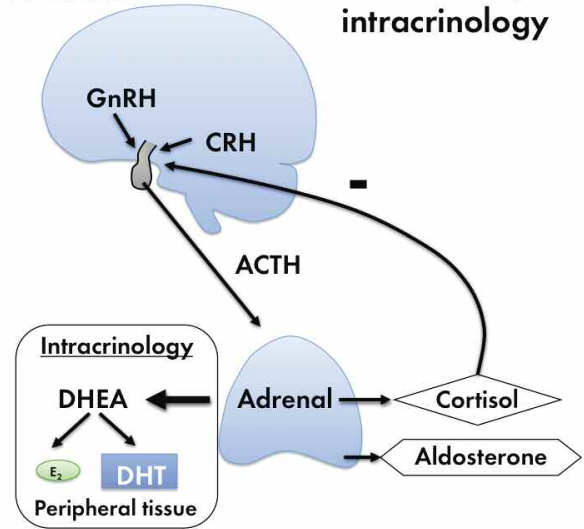
An important observation is that despite the arrest of estrogen secretion in all women at the time of menopause, not all postmenopausal women suffer from menopausal symptoms. Consequently, the hormonal difference between postmenopausal women with vaginal atrophy symptoms and those without (approximately 75% and 25%, respectively) is not related to estrogens. In fact, the only remaining hormonal difference between these two groups of women is the difference in the availability of DHEA, the exclusive source of sex steroids in postmenopausal women (Figure 3).

Therapeutic DHEA: Treatment for Postmenopausal Sex Steroid Deficiency

As a logical consequence of the facts

POSTMENOPAUSE

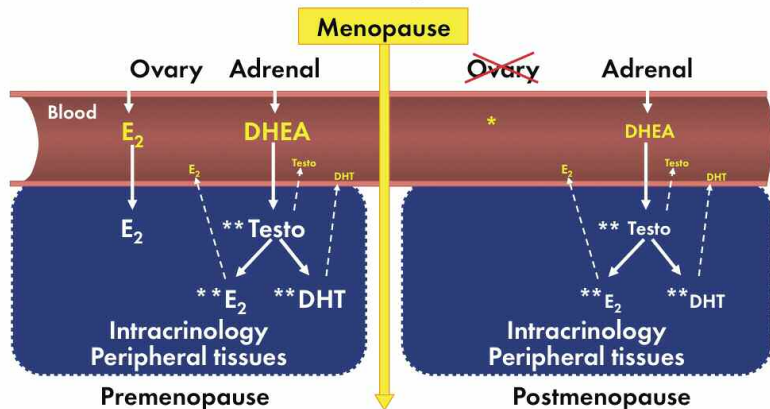
New findings: intracrinology



KEY: ACTH = adrenocorticotropic hormone; CRH = corticotropin-releasing hormone; DHT = dihydrotestosterone; E₂ = estradiol; GnRH = gonadotropin-releasing hormone

Figure 2. Schematic representation of the unique source of sex steroids in postmenopausal women, namely DHEA. After menopause, all estrogens and androgens are made locally from DHEA in peripheral target intracrine tissues. The amount of sex steroids made in peripheral target tissues depends upon the level of the steroid-forming enzymes specifically expressed in each tissue.⁴

Sources of estrogens in women



* No E₂ secretion in the blood after menopause and no significant systemic exposure
 ** E₂, testo and DHT made only in some specific tissues

KEY: ACTH = adrenocorticotropic hormone; CRH = corticotropin-releasing hormone; DHT = dihydrotestosterone; E₂ = estradiol; Testo= testosterone

Figure 3. Schematic representation of the major change in the source of estrogens at the time of menopause.

Rationale for DHEA

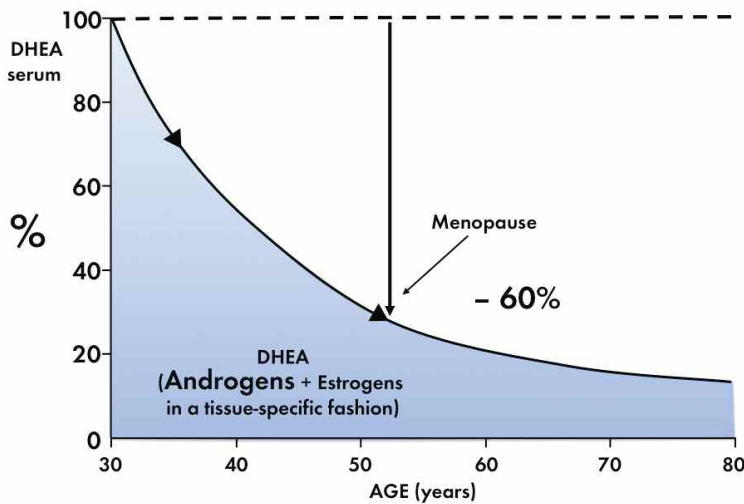


Figure 4. Schematic representation of the progressive decrease in serum DHEA with age. At time of menopause, serum DHEA has already decreased by 60% and the decrease continues thereafter. A parallel decrease is observed for total androgen exposure.

mentioned above, it can be postulated that DHEA replacement is the only possible treatment for sex steroid deficiency that obeys the laws of physiology after menopause. It is important to remember that a unique advantage of DHEA is that this inactive precursor or prodrug is transformed into active sex hormones (estrogens and/or androgens) only in the specific cells and tissues in need of these hormones. Due to the decreasing serum levels of DHEA with age (Figure 5), these tissues, however, make smaller and smaller amounts of sex steroids, thus causing symptoms in most, but not all, postmenopausal women. Supplementation with DHEA in symptomatic women simply mimics the situation of the higher DHEA activity present in healthy asymptomatic women.

Even if women continue to be exposed to relatively high serum levels of DHEA after menopause, it is well known that endometrial atrophy is a

physiologic consequence of menopause and is observed in all women.^{1,5} These findings are explained by the absence of enzymes, especially aromatase, able to transform DHEA into estrogens in the human endometrium.³⁵⁻³⁷

No Endometrial Effect

In agreement with this well-recognized observation of nature, the endometrial atrophy seen in all women at the start of treatment remained unaffected after 12 months of percutaneous DHEA administration, even when serum DHEA was increased by 13-fold.³³ Similarly, the Phase 3 ERC 210 study recently performed in 216 patients shows no effect on endometrial histology after 3 months of daily intravaginal DHEA.²² Moreover, no change in endometrial thickness was found after 6 months of daily oral DHEA (50 mg) in postmenopausal women.³⁸

Protection of the endometrium is the most obvious reason why evolution over 500-million years (Figure 6) has

succeeded in building an intracrine system unique to the human species and able to protect women from systemic exposure to estrogens after menopause. It is remarkable that while the steroidogenic enzymes appeared approximately 500-million years ago with the vertebrates, it is only about 50-million years ago that the adrenals of primates gained the ability to secrete large amounts of DHEA.³⁹ It is even more recently that DHEA of adrenal origin became practically the only source of sex steroids in women with the appearance of menopause. It therefore took more than 500-million years of evolution to separate the role of gonadal- and DHEA-derived sex steroids, thus permitting women to be free from the negative systemic effects of estrogens during all the postmenopausal years and, thus, benefit from a strictly tissue-specific formation and action of sex steroids made according to the specific age-related needs of each cell type in each tissue by the process of intracrinology.⁴

Sites of Tissue-Specific Action of DHEA

In addition to prostate and breast cancer, in which efficient blockade of the sex steroids made in peripheral tissues has provided major benefits with respect to cancer control and survival,⁴⁰⁻⁴² the documented intracrine formation of androgens and estrogens extends to non-malignant human diseases. The skin, for example, is an important target of intracrine sex steroid action.⁴³ In fact, it is well recognized that the skin synthesizes androgens from DHEA, and that acne, seborrhea, hirsutism and androgenic alopecia are associated with excess androgens.^{4,44} The observed stimulatory effect of DHEA on bone mineral density and the increase in serum osteocalcin, a marker of bone formation,³³ are of particular interest in the pre-

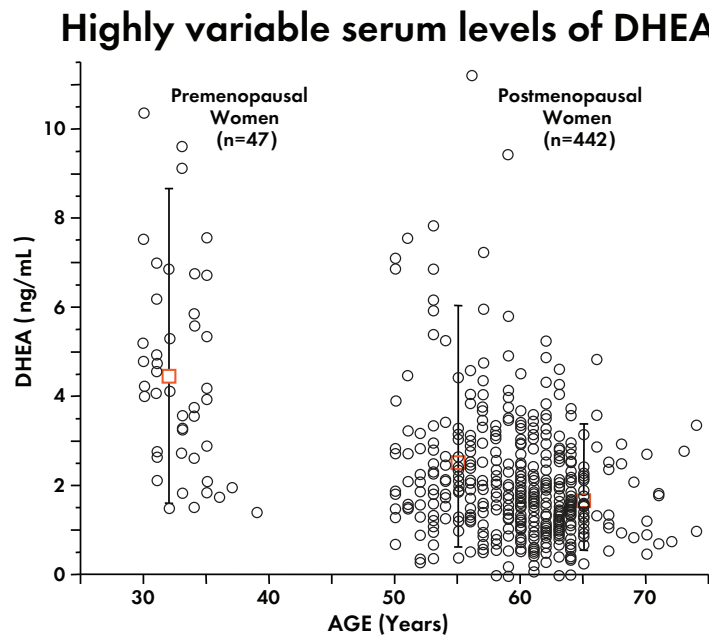


Figure 5. Illustration of the wide variability of serum DHEA levels in normal women ages 30 to 40 years and 50 to 75 years. Data are presented individually as well as by means and 5%-95% percentiles (Labrie et al, unpublished data).

vention and treatment of osteoporosis. These actions also indicate a unique activity of DHEA on bone (namely, a stimulation of bone formation) while ET, HT, bisphosphonates, selective estrogen-receptor modulators and calcitonin only reduce the rate of bone loss.

In a study performed in postmenopausal women who received a DHEA cream for 12 months, it was found that insulin resistance was decreased while subcutaneous fat was decreased and muscle mass was increased.³² Moreover, daily administration of 50 mg of DHEA for 6 months in 65- to 78-year old men and women decreased abdominal visceral fat in both women and men.⁴⁵ Furthermore, an improvement was observed in the insulin sensitivity index following DHEA administration.⁴⁵

As mentioned above, a review of a series of other studies³⁴ indicates that

beneficial effects of DHEA are exerted on bone formation, muscle loss, fat accumulation, skin atrophy and type 2 diabetes. All of the indications mentioned above, however, need large-scale, prospective, randomized placebo-controlled studies, as recently conducted for vaginal atrophy.^{22,23} The appropriate clinical trials should provide the scientific basis necessary to offer postmenopausal women the required safe and effective treatment of the hormone deficiency symptoms and signs of menopause without the risks reported in the Women's Health Initiative (WHI), the Million Women Study and a series of other studies conducted with estrogen-based formulations.

Vaginal Atrophy: Clear Example of DHEA Efficacy

Vaginal atrophy affects 50% of postmenopausal women from 50 to 60

years of age and 72% of women 70 years and older. In agreement with previous phase 2 data,^{26,33} it can be seen in Figure 7 that at the standard 12-week time interval, 0.5% DHEA caused a 45.9 ± 5.31 ($p < 0.0001$ versus placebo) decrease in the percentage of parabasal cells, a 6.8 ± 1.29 ($p < 0.0001$ vs placebo) increase in percentage of superficial cells, a 1.3 ± 0.13 unit ($p < 0.0001$ vs placebo) decrease in vaginal pH and a 1.4 ± 0.17 score unit ($p < 0.0001$) decrease in the severity of the most bothersome symptom. Similar changes were seen in vaginal secretions, color, epithelial surface thickness and epithelial integrity.²²

In addition to the effects of intravaginal DHEA on the symptoms and signs of vaginal atrophy, a time- and dose-dependent improvement in the four domains of sexual function was observed. At 12 weeks, the 1.0% DHEA dose, compared to placebo, led to 49% ($p = 0.0061$) and 23% ($p = 0.0257$) improvements in the desire domains in the Menopause Specific Quality of Life (MENQOL) and the Abbreviated Sex Function (ASF) questionnaires, respectively.²³ Compared to placebo, DHEA produced a 68% ($p = 0.006$) improvement in the ASF arousal/sensation domain, a 39% ($p = 0.0014$) improvement in the arousal/lubrication domain, a 75% ($p = 0.047$) improvement in orgasm, and a 57% ($p = 0.0001$) improvement in dryness during intercourse.²³ Vaginal DHEA applied daily at doses at which serum steroids remain well within normal postmenopausal values exerts potent beneficial effects on all four aspects of sexual dysfunction.^{23,25} Such data indicate that combined androgenic/estrogenic stimulation in the three layers of the vagina exerts important beneficial effects on sexual function in women without systemic action on the brain and other extravaginal tissues.

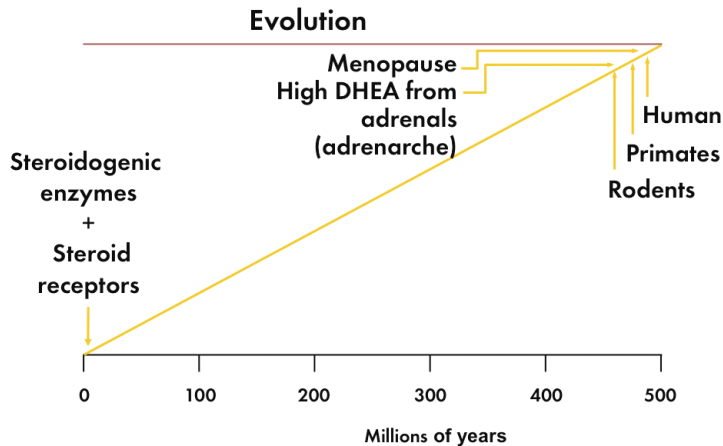


Figure 6. Schematic representation of the approximately 500-million years of evolution between the appearance of steroidogenic enzymes and the ability of the adrenals to synthesize high amounts of DHEA, a situation first seen in primates 50-million years ago. Protection of the uterus against unopposed estrogens is the most obvious reason for the cessation of estrogen secretion by the ovaries at menopause and the essential role of intracrinology which, in addition to providing each tissue with the physiological amount of sex steroids, protects tissues from systemic exposure to estrogens and androgens.

Role in the Three Layers of the Vagina

Our preclinical studies⁴⁶ have clearly demonstrated a very important local effect of DHEA not limited to estrogens, namely, stimulatory effect of the androgens derived from DHEA on collagen formation in the second layer of the vagina (lamina propria). This effect is supported by the recently described stimulatory effect of DHEA on collagen formation in the human skin dermis, the equivalent of the lamina propria in the vagina.⁴⁷

DHEA thus induces mucification of the epithelium or superficial layer of the vaginal mucosa, increases the density of the collagen fibers in the second layer (lamina propria) and stimulates the muscular third layer. Since the strength of the vaginal wall is largely dependent upon the collagen structure, and because collagen formation is exclusively stimulated by androgens

derived from DHEA in the lamina propria fibroblasts, DHEA plays an essential role in vaginal physiology and in the correction of vaginal atrophy symptoms and signs. Estrogen-based preparations, on the other hand, cannot correct the deficiencies related to the specific lack of androgens in postmenopausal women. Consequently, estrogens are only a partial treatment for vaginal atrophy.

Intravaginal Administration

Most importantly, no significant leakage of the active sex steroids into the circulation occurs with VAGINORM (0.5% DHEA or Prasterone),²⁶ thus explaining the highly beneficial vaginal effects observed in the absence of significant changes in circulating estrogens or androgens.^{22,23,25,26} In fact, as mentioned above, the active steroids are inactivated locally before being released as inactive metabolites into the general circulation,

from which they are eliminated by the kidneys and liver. On the other hand, all estrogen-based vaginal formulations increase serum estrogens.⁴⁸

Safety of DHEA Replacement Therapy

There is no reason to believe that the metabolism, action and safety of exogenous DHEA given at physiologic doses to symptomatic women would be different from the metabolism and action of endogenous DHEA in women who have sufficient levels of DHEA to remain free from the symptoms of menopause. Consequently, women with symptoms of vaginal atrophy and receiving DHEA are not different, hormonally speaking, from normal postmenopausal women having sufficient endogenous DHEA to remain asymptomatic. This is well supported by the absence of DHEA-related safety issues in the medical literature, in which high doses of DHEA have been used orally or percutaneously in a large series of women for up to 2 years.⁴⁹ Moreover, the data from the US FDA Adverse Event Reporting System and the Center for Food Safety and Applied Nutrition postmarketing database have not revealed any significant DHEA-related negative effect.

Summary and Conclusions

While the complete absence of ovarian estrogen secretion in postmenopausal women was previously believed to be the cause of all menopausal symptoms, the new understanding of intracrinology^{4,5} clearly demonstrates that a difference in DHEA blood levels, intratissular DHEA transformation, tissue sensitivity to sex steroids or a combination of these factors is responsible for the hormone deficiency symptoms and signs observed in women after menopause. The highly sophisticated mechanism of intracrinology

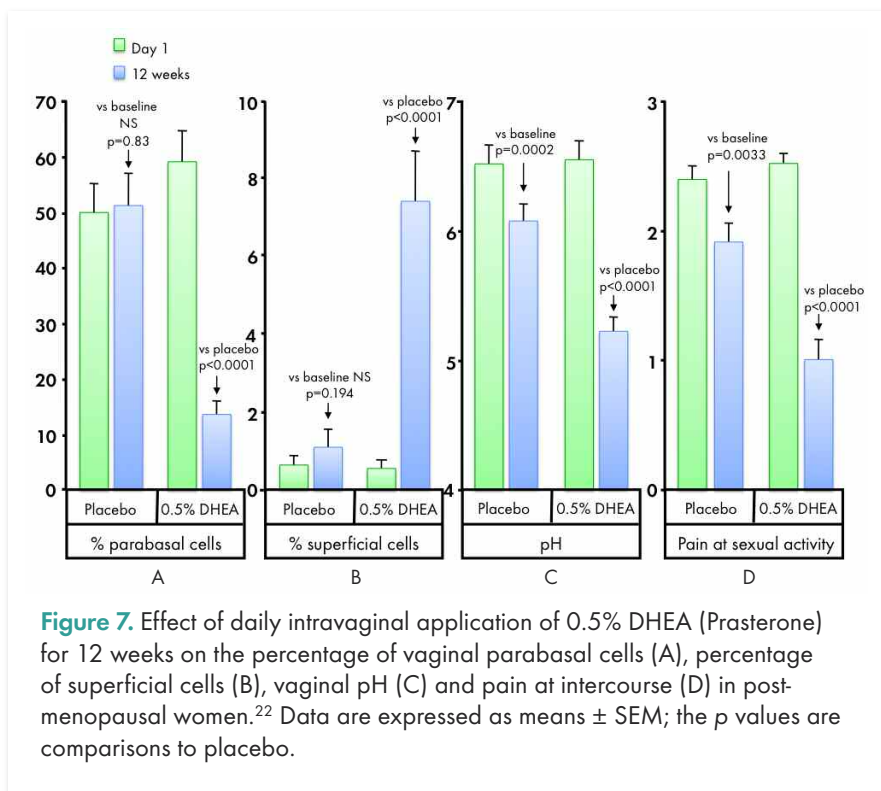


Figure 7. Effect of daily intravaginal application of 0.5% DHEA (Prasterone) for 12 weeks on the percentage of vaginal parabasal cells (A), percentage of superficial cells (B), vaginal pH (C) and pain at intercourse (D) in postmenopausal women.²² Data are expressed as means \pm SEM; the *p* values are comparisons to placebo.

has been achieved by the forces of evolution in operation for approximately 500-million years in order to avoid indiscriminate exposure of all tissues to estrogens in women.

Cessation of estrogen secretion by the ovaries is a physiologic phenomenon common to all women, thus preventing the adverse effects of estrogens, especially cancer of the uterus and possibly other negative effects in other tissues. Since this law of nature is now well understood and clearly demonstrated in prospective randomized and placebo-controlled clinical trials, especially in women suffering from vaginal atrophy and sexual dysfunction,^{22,23} the opportunity to apply this new knowledge to the treatment of the other problems related to sex steroid deficiency in postmenopausal women warrants further study.

Based upon the new understanding of the endocrine physiology of normal women, the objective is to develop a tissue-specific prehormone replace-

ment therapy that can provide the physiologic ratio and amount of androgens and/or estrogens only in the cells and tissues in physiologic need of these hormones, while avoiding exposure of the other tissues and the associated side effects reported in the WHI, Million Women Study and a series of other studies.²²

It is important to indicate that while ovarian secretion of E_2 is rigorously controlled by a negative feedback mechanism (Figure 1), such a control does not exist for the secretion of DHEA. In fact, DHEA secretion by the adrenals is controlled exclusively by adrenocorticotropin of anterior pituitary origin, which, in turn, is exclusively regulated by the circulating levels of cortisol, with no influence of DHEA (Figure 2). This means that a decrease in serum DHEA levels does not trigger increased endogenous DHEA secretion in a manner analogous to the decreased serum cortisol levels that trigger increased secretion of

ACTH (Figure 2). The consequence is that when serum DHEA decreases in women with age or for any other reason, there is no endogenous compensatory mechanism to increase DHEA secretion by the adrenals and permit a return of serum DHEA to normal levels. Consequently, the only possible means of providing postmenopausal women the amount of DHEA needed to treat their menopausal symptoms is to administer a physiologic amount of exogenous DHEA, which is metabolized and acts exactly like endogenous DHEA. In fact, as mentioned above, symptomatic women receiving a physiologic amount of DHEA as replacement therapy for symptoms of sex steroid deficiency should not be different, hormonally speaking, from the group of women who secrete DHEA at a sufficient level to be free of menopausal symptoms, thus practically eliminating safety issues. After menopause, about 25% of postmenopausal women do not develop menopausal symptoms because these women have sufficient levels of endogenous DHEA activity to remain free of symptoms.

Of interest is that saturation of the enzymatic systems that transform DHEA into active androgens and/or estrogens is observed at serum levels of about 7 ng DHEA/mL, thus protecting women against potential excess levels of sex steroids.⁵⁰ We believe that natural saturation of the enzymatic mechanisms responsible for the transformation of DHEA into estrogens and androgens makes it practically impossible to administer a dose of DHEA that could be high enough to potentially lead to excess tissue exposure to estrogens and/or androgens. The fact that no serious adverse event has ever been observed following treatment with DHEA could well be explained, at least partially, by this self-protecting mechanism. Based on the information men-

tioned above, it is reasonable to believe that no adverse effect is expected from replacement with DHEA, a pre-hormone free of intrinsic sex steroid activity, and requiring tissue-specific transformation before sex steroid activity can be exerted. Of course, further efficacy studies and accompanying safety evaluation remain essential. ■

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This article includes discussion of off-label use of medication.

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