

Gynecology

Delivery of dehydroepiandrosterone to premenopausal women: Effects of micronization and nonoral administration

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OBJECTIVES: This single-dose study compares three dehydroepiandrosterone delivery methods (oral crystalline steroid, micronized steroid, and vaginal administration) to ascertain whether physiologic levels of circulating dehydroepiandrosterone and dehydroepiandrosterone sulfate can be obtained while increases in testosterone are minimized.

STUDY DESIGN: Two randomized, double-blind, placebo-controlled single-dose comparisons were made. For oral micronized versus crystalline dehydroepiandrosterone 300 mg doses of micronized or crystalline dehydroepiandrosterone were administered, followed by 6 hours of blood sampling ($n = 7$). Serum dehydroepiandrosterone, dehydroepiandrosterone sulfate, and testosterone levels were measured; areas under the curve and mean peak values were analyzed by Student -Newman-Keuls tests. For oral versus vaginal micronized dehydroepiandrosterone 150 mg oral or vaginal doses of micronized dehydroepiandrosterone were administered, followed by blood sampling over 12 hours ($n = 5$). Data analysis was as described.

RESULTS: Oral micronized and unmicronized dehydroepiandrosterone resulted in increases in serum dehydroepiandrosterone, dehydroepiandrosterone sulfate, and testosterone. Micronization increased the area-under-the-curve ratios for dehydroepiandrosterone sulfate/dehydroepiandrosterone and dehydroepiandrosterone

sulfate/testosterone. Vaginal administration provided equivalent serum dehydroepiandrosterone; however, it failed to increase dehydroepiandrosterone sulfate or testosterone over placebo.

CONCLUSION: Micronization of oral dehydroepiandrosterone diminishes bioconversion to testosterone. Vaginal dehydroepiandrosterone delivers equivalent dehydroepiandrosterone but substantially diminishes dehydroepiandrosterone bioconversion. (AM J OBSTET GYNECOL 1996;174:649-53.)

Key words:

Dehydroepiandrosterone

administration

dehydroepiandrosterone

micronization

dehydroepiandrosterone

vaginal administration

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The adrenal androgens dehydroepiandrosterone (DHEA) and its sulfated cognate, dehydroepiandrosterone sulfate (DHEA-S), are believed important regulators of body fat,^[1] immune function,^[2] insulin sensitivity,^[3] and circulating lipoproteins.^[4] They may confer protection against diseases of aging, such as atherosclerosis,^[4] osteoporosis,^[5] and cancer.^[6] DHEA-S also acts as a circulating precursor for ovarian steroidogenesis.^[7] DHEA and DHEA-S decline with age^[8] ("adrenopause"), hypopituitarism,^[9] and adrenal insufficiency,^[10] in association with glucocorticoid administration,^[11] and in chronic wasting diseases.^[12] DHEA supplementation may be of value in ameliorating conditions aggravated by deficient adrenal androgen secretion. There is, however, only limited information on systems for DHEA delivery to premenopausal women.

In preliminary investigations^[13] oral DHEA administration in large doses produced high circulating testosterone (T) and dihydrotestosterone levels with associated atherogenic lipoprotein changes, increasing insulin resistance and decreasing sex hormone-binding globulin. A method of attenuating biotransformation of DHEA to T and dihydrotestosterone would thus enhance the potential of DHEA as a therapeutic agent. Strategies to attenuate this effect include (1) decrease in DHEA dose to

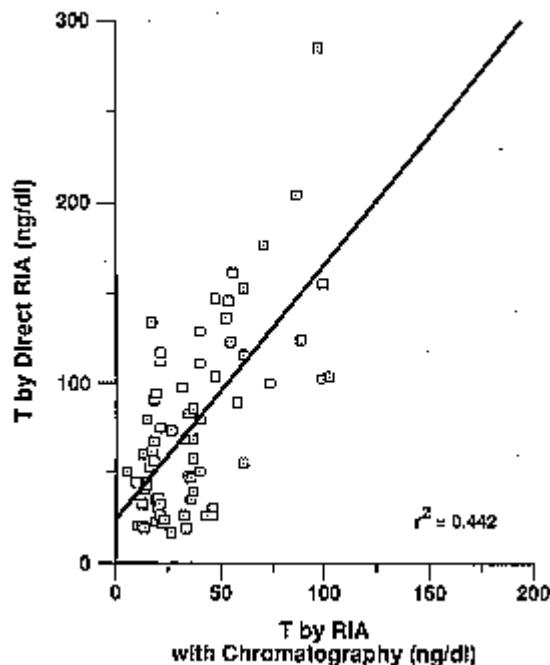


Figure 1. Correlation between direct double-antibody T radioimmunoassay and chromatographic assay. Direct assay overestimates serum T values by 47% (by linear regression).

provide only enough bioavailable steroid to recreate a physiologic adrenal androgen milieu, [14] (2) micronization to modify hepatic first-pass metabolism, [14] or (3) nonoral (i.e., vaginal) administration to bypass the portal system.

This single-dose study compares three delivery methods (oral crystalline steroid, micronized steroid, and vaginal administration) to ascertain whether physiologic levels of circulating DHEA and DHEA-S can be obtained while increases in T are minimized. We tested the following hypotheses: (1) that oral micronized DHEA delivers a higher increment of circulating DHEA and DHEA-S relative to T than the unmicronized crystalline product and (2) that vaginal DHEA, in bypassing the portal circulation, attenuates biotransformation to T.

Material and methods

The first part of this study compares micronized or crystalline oral DHEA bioavailability. The second part compares oral versus vaginal micronized DHEA. Institutional review board approval was obtained before the study.

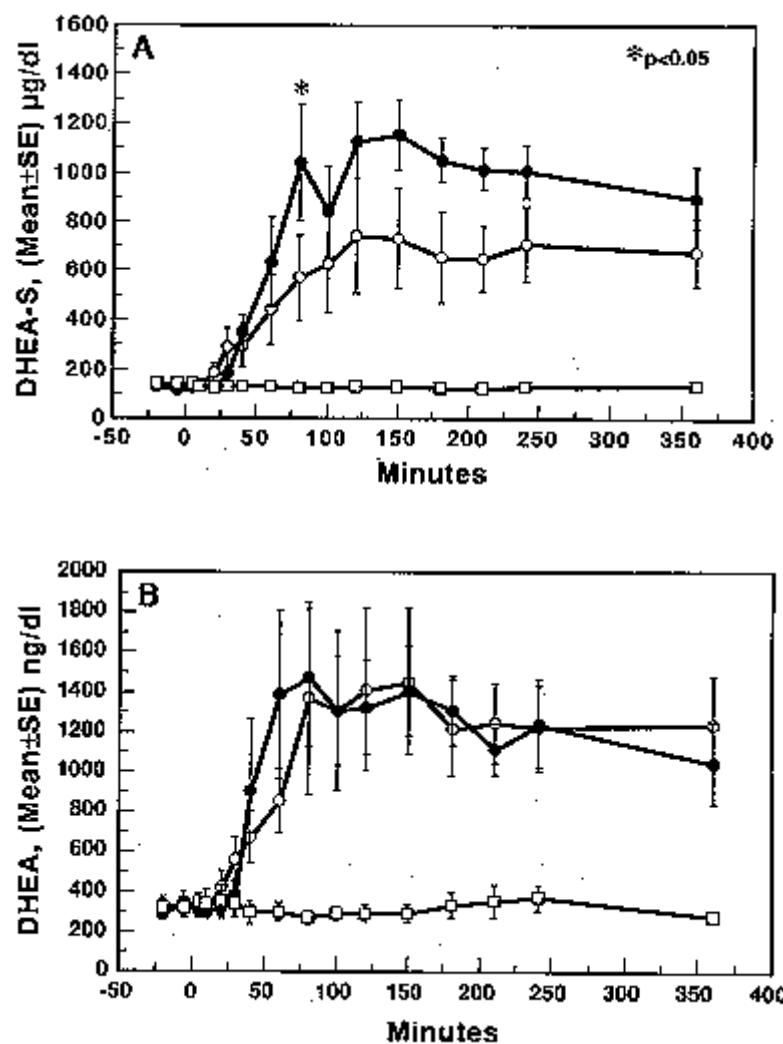
Oral micronized versus crystalline DHEA

Study subjects.

Seven healthy, nonsmoking, normal-weight, regularly menstruating, premenopausal women (Table I) were studied. None were taking other medications. Inclusion criteria included normal screening cortisol, DHEA, DHEA-S, and T levels, thyroid and liver functions, complete blood count, fasting serum insulin level, and serum lipoprotein level.

DHEA preparation.

Pharmacopoeia-grade DHEA (Sigma Chemical Company, St. Louis) was micronized and compounded into DHEA tablets containing 300 mg per dose in a wax -vegetable oil matrix, with a silica-based



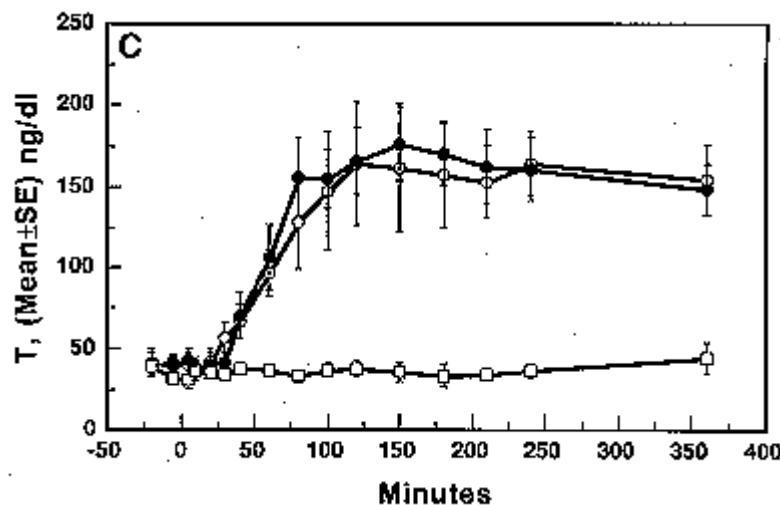


Figure 2. Pattern of serum DHEA-S (A), DHEA (B), and T (C) after oral administration of 300 mg micronized or crystalline DHEA or placebo ($n = 7$). At 80 minutes serum DHEA-S was significantly higher with micronized than with crystalline preparation. Crystalline DHEA (---), micronized DHEA (- - -), and placebo (---).

excipient (Belmar Pharmacy, Lakewood, Colo.). Identical crystalline DHEA and placebo tablets were also made.

Experimental design.

Single oral doses of micronized, crystalline, or placebo tablets were administered to the subjects in random sequence during the midfollicular phase of the menstrual cycle. Subjects fasted for 8 hours before and 3 hours after administration; a standard light meal was then provided. Intravenous access was established

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TABLE I -- Subject screening data

| | Oral micronized crystalline (300 mg DHEA) ($n = 7$) | | Oral/vaginal (150 mg micronized DHEA) ($n = 5$) | |
|--|---|------------|---|-----------|
| | Mean | Range | Mean | Range |
| Age (yr) | 33.3 | (22-42) | 26 | (21-35) |
| Percent ideal body weight ^a | 99.6 | (89-112) | 96.4 | (89-100) |
| DHEA-S (μg/dl) | 130.4 | (99-191) | 200.6 | (104-261) |
| Cortisol (9 AM, ng/dl) | 12.2 | (7.9-20.8) | 12.5 | (6.1-25) |
| T (ng/dl) | 41.1 | (32-58) | 66.8 | (31-99) |

^aMetropolitan Life Insurance Tables.

30 minutes before administration, and blood samples were drawn at -20, -5, 5, 10,

20, 30, 40, 60, 80, 100, 120, 150, 180, 210, 240, and 360 minutes after the dose. Serum was frozen and batch assayed for DHEA, DHEA-S, and T.

Vaginal versus oral micronized DHEA

Study subjects.

Five healthy, normal-weight, nonsmoking, nonmedicated, premenopausal women were studied ([Table I](#)).

Experimental design.

Tablets of 150 mg micronized DHEA and matching placebos were randomly administered either vaginally or orally at 8 AM in random order. When the tablets were given vaginally, the subjects placed them high in the posterior fornix of the vagina and remained fasting and recumbent for 3 hours. Limited movement and a light meal were then allowed. Blood was drawn over a more extended time frame (at -20, 5, 15, and 30 minutes and at 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, and 12 hours). Serum was frozen and later batch assayed for DHEA, DHEA-S, and T.

Steroid assays.

Serum DHEA was measured by use of a tritiated extraction assay (Wein Scientific, Succasanna, N.Y.). Serum DHEA-S and T were measured with iodinated direct double-antibody assays (Pantex, Santa Monica, Calif.). All samples from each patient were measured in the same assay; all intraassay coefficients of variation were <9%.

Because of overestimation of T in the direct assay a range of T values in both experiments ($n = 70$) were identified and the samples were reassayed with a validated in-house chromatographic assay. ^[15] The degree by which the direct assay overestimates the T values was determined by linear regression ([Fig. 1](#)). With a high degree of correlation ($r = 0.666$) the direct assay overestimates the chromatographic assay by 47% (linear regression).

Statistical analysis.

For each steroid the mean concentrations achieved at each time point for each of the preparations were compared by means of analysis of variance followed by Student-Newman-Keuls tests.

For each steroid and for each subject the areas under the 6- or 12-hour curve were then determined. Mean areas-under-the-curve were calculated, and the existence of significant differences between treatment

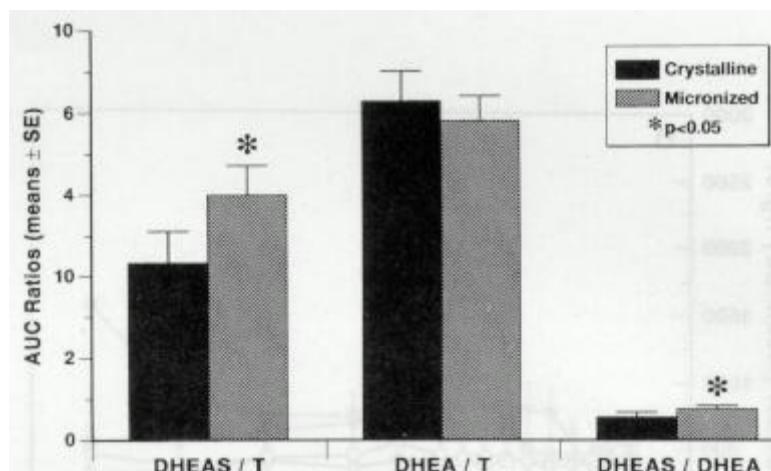


Figure 3. Ratios of areas-under-the-curve for DHEA-S, DHEA, and T after oral administration of 300 mg of micronized or

unmicronized DHEA or placebo ($n = 7$). DHEA-S/T and DHEA-S/DHEA ratios are significantly increased with micronization.

arms for the mean areas-under-the-curve of each steroid was determined according to Student -Newman-Keuls tests.

Similarly, peak DHEA, DHEA-S, and T concentrations after administration were identified; mean peak values were then calculated. For each hormone and for each treatment mean peak values were compared for significant differences with Student -Newman-Keuls tests.

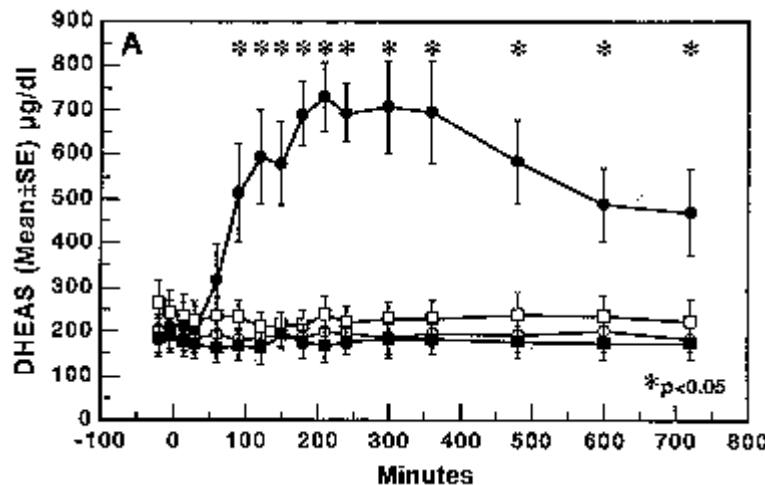
Further analysis of the oral micronized versus crystalline comparison was performed with the calculated areas-under-the-curve. The results for each arm were expressed as the ratios DHEA-S/T, DHEA/T, and DHEA-S/DHEA and analyzed to detect differences in downstream androgenic metabolites after each treatment.

Results

Micronized versus crystalline oral DHEA (300 mg).

The patterns of serum DHEA-S, DHEA, and T after oral administration are shown in [Fig. 2](#) , A, B, and C. Significant enhancement of serum DHEA-S levels was obtained with the micronized form over the crystalline preparation only at 80 minutes. However, at all time points after 40 minutes the micronized preparation had higher DHEA-S levels. For both micronized and unmicronized DHEA areas-under-the-curve and mean peak values for serum

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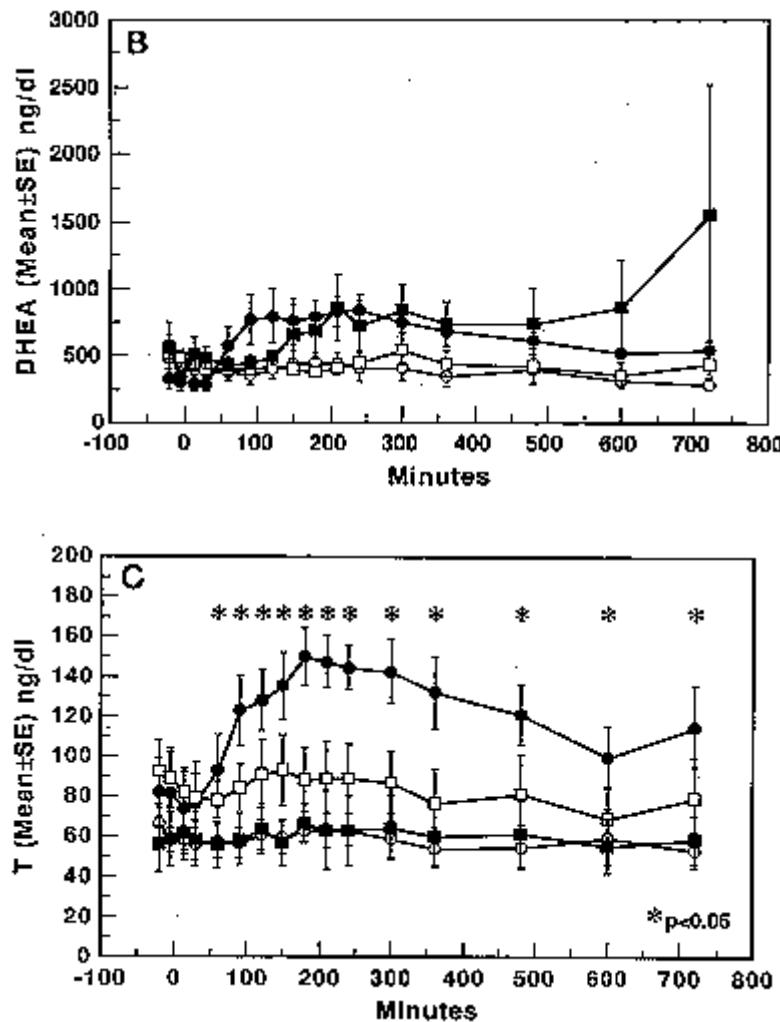


Figure 4. Serum DHEA-S (A), DHEA (B), and T (C) levels after oral or vaginal administration of 150 mg micronized DHEA or placebo (n = 5). Significant elevation of serum DHEA-S and T levels is seen with oral over vaginal DHEA preparation after 90 and 60 minutes, respectively. Oral placebo (---), oral micro-nized DHEA (---), vaginal placebo (---), vaginal micro-nized DHEA (---).

DHEA, DHEA-S, and T all rose significantly above placebo ($p < 0.05$), with no significant differences between treatments.

The mean area-under-the-curve DHEA/S/DHEA ratio, however, was significantly increased ($p < 0.05$) after micronized

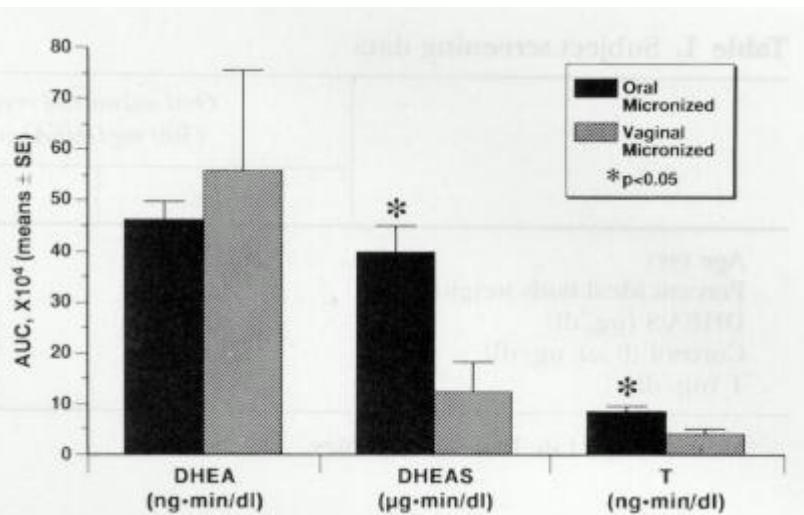


Figure 5. Areas-under-the-curve for DHEA, DHEA-S, and T after vaginal or oral administration of 150 mg of micronized DHEA ($n = 5$). There is no significant bioconversion of vaginally administered DHEA to DHEA-S or T, but delivery of DHEA is similar to that obtained with oral administration.

DHEA over the unmicronized preparation (Fig. 3). Similarly, the mean area-under-the-curve DHEA-S/T ratio also increased ($p < 0.05$) after micronized DHEA. There was no difference between the two preparations in the area-under-the-curve DHEA/T ratio.

Vaginal versus oral micronized DHEA (150 mg).

The pattern of serum steroids obtained with oral or vaginal micronized DHEA versus placebo is presented in Fig. 4, A, B, and C. From this figure it is apparent that serum DHEA-S and T levels were significantly enhanced with the oral form over the vaginal DHEA preparation, respectively, from 90 and 60 minutes after administration on. Micronized oral DHEA also resulted in significant ($p < 0.05$) increases in areas-under-the-curve and mean peak values for DHEA, DHEA-S, and T over placebo. However, after vaginal DHEA administration, whereas the increase in DHEA was comparable to that with oral administration at the same dose, areas-under-the-curve and mean peak values for DHEA-S and T did not increase over those with placebo. Thus areas-under-the-curve and mean peak values for DHEA-S and T after oral DHEA were significantly higher ($p < 0.05$) than with vaginal DHEA (Fig. 5).

Comment

This study demonstrates that both micronization and vaginal administration modify absorption and biotransformation of exogenous DHEA in premenopausal women. Micronization increased the circulating DHEA-S disproportionately to DHEA and T and may therefore provide an advantage in increasing a potentially bioactive pool of circulating nonandrogenic prehormone (DHEA-S) with attenuated conversion to T.

Supraphysiologic elevations were also seen in the serum DHEA-S, DHEA, and T levels after administration of the micronized and crystalline preparations. For both, mean peak serum T levels with the direct T assay were approximately 200 ng/dl. Given that this assay overestimates serum T by 47%, by inference, a 50 mg oral dose of oral micronized or unmicronized DHEA once a day to

premenopausal women with low endogenous adrenal androgens may be adequate to elevate serum DHEA-S to the upper normal range, with only slight elevation of T.

Vaginal DHEA produces a metabolic pattern differing strikingly from that with oral dosing. Despite serum DHEA time-concentration curves equivalent to those with oral administration, post -vaginal administration DHEA-S and T areas-under-the-curve and mean peak values did not differ from those for placebo. Thus, even though peak serum DHEA attained with vaginal administration was supraphysiologic, no significant transformation to T or DHEA-S was observed with one dose. Whereas it is difficult to extrapolate these findings to changes that might occur with multidose administration, it is clear that one-time vaginal administration readily produces elevated circulating DHEA yet greatly diminishes biotransformation to T and DHEA-S. Direct systemic administration (e.g., transcutaneous, parenteral, or vaginal) may thus ultimately represent an alternate way of administering this hormone. Whether this confers significant therapeutic advantage awaits further study.

We have previously described successful low-dose DHEA replacement in postmenopausal women. ^{[2] [3] [14]} Given that many of the salutary effects of DHEA may also be operative before menopause and that DHEA-S is a circulating prehormone of ovarian follicular sex steroidogenesis, ^[2] low-dose administration of this hormone to premenopausal women may be beneficial in situations where endogenous adrenal androgen secretion is low, such as in hypopituitarism, in adrenal insufficiency, or with glucocorticoid administration. Demonstration of the beneficial effects of micronization and vaginal administration opens avenues of research to address more directly the promising issues surrounding physiologic DHEA replacement in premenopausal women.

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