Should Dehydroepiandrosterone Be Administered to Women?

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Context: Androgen prohormones such as dehydroepiandrosterone (DHEA) increase in early puberty, peak in the second and third decade, and thereafter decline, independent of menopausal status. Investigators have examined their potential beneficial effects in normal women and those with DHEA-deficient states.

Evidence Acquisition: A review of the literature from 1985 to 2021 on the potential benefits and risks of androgen prohormones in women.

Evidence Synthesis: Studies have examined the potential benefit of DHEA therapy for anti-aging, sexual dysfunction, infertility, metabolic bone health, cognition, and wellbeing in hormone-deficient states such as primary adrenal insufficiency, hypopituitarism, and anorexia as well as administration to normal women across the lifespan.

Conclusions: Data support small benefits in quality of life and mood but not for anxiety or sexual function in women with primary or secondary adrenal insufficiency or anorexia. No consistent beneficial effects of DHEA administration have been observed for menopausal symptoms, sexual function, cognition, or overall wellbeing in normal women. Local administration of DHEA shows benefit in vulvovaginal atrophy. Use of DHEA to improve induction of ovulation response in women with diminished ovarian reserve is not recommended. Risks of high physiologic or pharmacologic use of DHEA include androgenic and estrogenic side effects which are of concern for long-term administration.

Clinical Case: A 49-year-old woman with Addison’s disease who is on low dose estrogen with cyclic progesterone therapy for menopausal symptoms returns for follow-up. She is on a stable glucocorticoid replacement strategy of hydrocortisone 10 mg in the morning and 5 mg in the early afternoon and fludrocortisone 0.05 mg each morning. She has read on the internet that additional therapy with DHEA may help her overall quality of life and libido. She asks whether she should add this therapy to her regimen and at what dose.

Key Words: DHEA, androstenedione, testosterone, hormonal therapies

Abbreviations: ACTH, adrenocorticotropin; DHEA, dehydroepiandrosterone; DHEAS, dehydroepiandrosterone sulfate; PPARα, peroxisome proliferator activated receptor α

Physiology of Androgen Prohormones: DHEA and Androstenedione

The pathway of adrenal steroidogenesis is reviewed in Fig. 1. Importantly, dehydroepiandrosterone (DHEA), DHEA sulfate (DHEAS), and androstenedione are not themselves androgens but instead prohormones that are converted to testosterone and/or estradiol in target tissues to act on the respective steroid receptors. DHEA was originally extracted from male urine and human plasma in the 1930s and 1950s, respectively, and the sulfated form, DHEAS, was detected in 1944 (reviewed in (1, 2)). Baulieu and coworkers established that DHEAS was the most abundant steroid hormone precursor circulating in plasma (3). In addition, in the brain, DHEA and/or its metabolites may act as neurosteroids via membrane receptors such as gamma aminobutyric acid alpha and N methyl-D aspartate receptors or has been postulated to interact with the peroxisome proliferator activated receptor (PPARx), pregnane X receptor, androstanol, or estrogen receptor β to have central and metabolic effects (reviewed in (2)). Studies suggested a role for DHEA in the immune system or in improving immune response with aging, but no clinical outcome studies have been reported (4, 5). No specific, high-affinity physiologic DHEA receptor has been identified (2).

DHEA is produced in the zona reticularis of the adrenal gland DHEAS is the most abundant prohormone for steroid hormones is also predominantly made in the adrenal or converted from DHEA in the liver and intestines (6). Whereas DHEA is released in an episodic fashion with a shorter half-life and modulated by stress and exposure to glucocorticoids, DHEAS has a longer half-life and stable levels across the day. In target tissues, DHEA is metabolized to androstenediol, androstenedione, testosterone, dihydrotestosterone, and 17β-estradiol (7). Androstenedione production is derived both from the adrenal gland and the ovary (8). These adrenally produced hormones are precursors for 30% of androgens in men, and 75% in premenopausal and 100% in postmenopausal women (9). DHEA and DHEAS levels increase across adrenarche during the pubertal process before gonadarche and peak in the late 20s to 30s before declining with age independent of menopausal status (9, 10).

Recently the role of 11-oxygenated adrenal prohormones has been investigated for their role in adrenarche and in states of adrenal androgen excess such as premature pubarche, congenital adrenal hyperplasia and adrenal tumors (11, 12). An abundant unconjugated androgen produced by the adrenal glands is 11β-hydroxyandrostenedione. One of its byproducts,
11-ketotestosterone, is produced locally in peripheral tissues; together with its 5α-reduced downstream product, 11-ketodihyrdrotestosterone, they have been shown to be bioactive androgens with potencies similar to testosterone. These 11-oxyandrogens peak in midlife but do not decline with age (11). Their role in adrenal androgen–“deficient” states or effects of supplementation have not been investigated to date.

One of the issues as we review the literature or consider DHEA supplementation is what is the physiologic dose of this hormone in women? The fact that DHEA and other prohormones are currently available over the counter as supplements in the United States or via the internet without FDA oversight for potency or duration of action is a major issue. DHEA is widely available as a dietary supplement in the United States; however, quality control of DHEA or androstenedione has been shown to be inconsistent (13). Therapeutic regimens in clinical trials have usually given DHEA administered in physiologic doses of 25 to 50 mg/day; however, some studies examined pharmacologic dosing up to 1600 mg/day (14). Based upon the pharmacology of DHEA, the supplementation dose should be 25 mg in postmenopausal women and 50 mg in men (15).

**Disorders for Which Androgen Prohormones Have Been Administered**

The effects of DHEA administration in physiologic to pharmacologic doses has been examined in women with low DHEA levels, namely deficient states such as primary and secondary insufficiency and anorexia, as well as supplementation to those women with normal DHEA levels for various potential health outcomes. This review will distinguish between these interventions and conclude an overall lack of data to support DHEA administration to most women.

**DHEA Therapy in DHEA Nondeficient States**

**Anti-aging Promotion for DHEA**

The abundance of the adrenal precursors, and their decline with aging and with exposure to exogenous glucocorticoids has raised the potential for their supplementation as an “anti-aging” prescription (3). Mortola and Yen performed initial studies in 17 women aged 40-70, given DHEAS 50 mg nightly for 3 months in a placebo-controlled, crossover study and reported an 84% increase in physical and psychological wellbeing in women, but no change in libido (16). A 2-fold increase in androstenedione, testosterone, and dihydrotestosterone levels was detected without change in estradiol. Baulieu and colleagues examined the administration of synthetic DHEA at 50 mg daily in 280 older women and men (ages 60-79, 140 each) without adrenal insufficiency for a year in the DHEAge study (17). Increases in testosterone and estradiol were observed in the women at 6 months with 21% of values outside the normal premenopausal range. The androgens decreased by 12 months, whereas estradiol remained consistently increased from baseline (17). The authors postulated an adaptive mechanism with time to limit the potential androgenic side effects long term, but which was not seen with the elevation in estradiol which persisted. These observations are important to consider with any long-term DHEA therapy in postmenopausal women. Improvement in sexual function was reported, but only 25% of the subjects understood the visual analog scale and extent of response was variable at 6 or 12 months (17). The authors posited a potential effect of changes in estradiol on these sexual outcomes in women. No effects on libido or sexual function were observed in men (17). In addition, there were no effects on muscle strength with this year-long intervention in older women aged 60-80 (18). More recently, investigators performed a 2-year, placebo-controlled, randomized, double-blind study in 57 elderly women with low DHEA levels. In the 27 women who received DHEA, there was a consistent increase in both testosterone and estradiol levels, but again no improvement noted in quality of life (19). Thus, these studies and others have argued against the use of DHEA as an anti-aging panacea for women. The potential long-term risks of DHEA administration to increase testosterone and estradiol levels in older women regarding estrogen-dependent malignancies and cardiovascular benefit or risk would also need to be considered.

**Cognition**

Because of the known deterioration in cognition with aging, several studies have examined the effects of supplementation on cognitive outcomes. Wolf and coworkers examined effects...
of DHEA after a stressor to examine its potential role as a neurocognitive protector (20). After 2 weeks of treatment, placebo group performance deteriorated significantly on a test of selective attention following a psychosocial stressor \( (P < .05) \), while deterioration was not evident in the DHEA group \( (P = .85) \). DHEA was associated with significant impairment on a visual memory recall test \( (P < .01) \) following the stressor. No significant effects were found on a third cognitive task. In contrast, Nair et al enrolled 57 women with low DHEAS levels in a 24-month study and no significant changes in quality of life measures were found (19). In 2008, von Muhlen administered DHEA for 1 year and showed no significant benefit on cognition performance in 225 healthy older people (21). Reduced performance in a visual memory recall test observed in 1 trial and a significant drop-out rate in favor of placebo emerged in another trial (21). Work by our group in a small study to understand how DHEA alters steroid hormone levels across the day demonstrated that after administration of DHEA to postmenopausal women, androgens increased transiently followed by estradiol levels, with a different impact on whichever specific cognitive outcome measure was randomly assessed across the day (22). Estrone levels were positively and androgen levels negatively associated with measures of recognition memory; however, the associations were reversed in perceptual identification tests (22). These results suggested that estrogens produced a positive effect on recognition memory, while androgens produced a negative effect. This pattern reversed in perceptual identification, with estrogens producing a negative effect and androgens producing a positive effect. The metabolism of DHEA across the day may explain its complex effects on cognition. The effects of DHEA supplementation may be direct on neurocognitive targets or indirect via metabolism to androgen or estrogen targets (2). In addition, the ability of specific cognitive measures to detect specific effects of DHEA administration may be complex, and individually variable. A Cochrane meta-analysis of 5 validated studies concluded there were no consistent effects of DHEA supplementation on cognitive outcomes (23). Thus, collectively, we have no data to support DHEA supplementation to older women for cognitive benefit.

What About Effects of DHEA in the Perimenopause and on Menopausal Symptoms?

Barnhart and coworkers performed a 3-month study in 60 perimenopausal women given DHEA 50 mg daily and demonstrated elevations in prohormone and testosterone levels and a 2-fold increase in estradiol levels (24). They reported no improvement in severity of perimenopausal symptoms, mood, dysphoria, libido, cognition memory, or wellbeing (24). A meta-analysis was performed to examine 16 trials in peri- and postmenopausal women; the quality of the studies was low to moderate. DHEA did not improve the quality of life, did not consistently affect menopausal symptoms and minor effects of sexual function compared with hormonal therapy, and was associated with androgenic side effects such as skin changes, acne, and hirsutism (25).

What About Use of DHEA Supplementation in Deficient States?

Adrenal insufficiency

Both primary adrenal insufficiency or secondary adrenocorticotropic (ACTH) deficiency with hypopituitarism results in long-term low or undetectable DHEA levels (26). In contrast, in isolated gonadal insufficiency, the androgen prohormones are usually normal as the major production of these hormones is the adrenal gland and peripheral conversion.

Initial studies of predominantly premenopausal women aged 23-59 with adrenal insufficiency by Arlt and colleagues \( (n = 24) \) given DHEA 50 mg daily or placebo for 4 months demonstrated improved wellbeing and decreased depression and anxiety. In addition, they noted an increased frequency of sexual thoughts, sexual interest, and satisfaction (27). Others administered micronizable DHEA 50 mg/day to 24 women aged 26-69 with Addison’s disease in a 3-month, crossover study. They observed a significant improvement in self-esteem and fatigue in the evening; however, they found no consistent effect on cognition or sexual arousal or function (28). Studies in 19 women with adrenal insufficiency given a lower dose of 25 mg of DHEA daily which restored levels to premenopausal range reported no improvements in wellbeing or sexual function and yet a high rate of side effects, including sweat odor and scalp itching, even with this lower dose (29). Gurnell and coworkers administered DHEA 50 mg daily to 32 women with adrenal insufficiency for a longer term 12 months and noted no improvement in fatigue, cognitive or sexual function (30). In addition, high DHEAS levels were observed in women with some androgenic side effects. Thus these data overall do not support a consistent beneficial effect of DHEA administration to women with adrenal insufficiency.

Studies in women with hypopituitarism reported variable outcomes in quality of life, sexual function, or improved mood. Administration of DHEA 25 mg to adolescent girls with central ACTH deficiency increased pubic hair and improved wellbeing (31). However, Johannsson and coworkers administered DHEA in an age-based dosing of 20 mg to 50 mg daily to 38 women with hypopituitarism for 6 months in an open-label, crossover design and observed no significant improvement in quality of life, and sexual interest or activity (32). In later studies, authors asked whether adding DHEA to growth hormone therapy was beneficial. DHEA administered at 50 mg daily for 4 months in a double-blind, placebo-controlled, crossover study did not improve quality of life (33).

A recent meta-analysis of 10 studies summarized that DHEA administration in women with primary or secondary adrenal insufficiency results in only small improvements in quality of life and mood (depression) but no significant consistent effects on anxiety or sexual function (34). DHEA at a dose of 50 mg to premenopausal women with hypopituitarism women restores androgen prohormones and testosterone to normal or often high levels. The role of variable estrogen replacement therapy in these studies may have impacted the variability in the results.

Anorexia nervosa

There are profound effects on the endocrine system in women with anorexia (35). Investigators examined the effects of DHEA 50 mg daily for potential beneficial effects in premenopausal women with anorexia on wellbeing and bone density. In 30 women randomized to DHEA 50 mg daily compared with standard hormonal therapy with an oral contraceptive for a year, they noted that patients receiving DHEA exhibited improvement on 3 validated psychological instruments (Eating Attitudes Test, Anorexia Nervosa Subtest, and Spielberger Anxiety Inventory)
DHEA administration also improved bone turnover markers. In another small study, DHEA resulted in resumption of menses in 50% of women via a hypothesized increase in estradiol levels (37). These data again support that DHEA action is via conversion to androgens and estrogens in different target tissues.

Other Areas Where DHEA Supplementation Has Been Promoted

Sexual dysfunction

In a systematic review and meta-analysis of 23 trials in 1188 postmenopausal women, DHEA therapy was not associated with an improvement in libido or other sexual function outcomes when compared with placebo (38). The Endocrine Society guidelines and recent international guidelines agree on the lack of data supporting the use of DHEA for sexual dysfunction (39-41).

Mood

Based upon initial reports of improvement in mood with administration of DHEA in those with adrenal insufficiency, authors have postulated that the effects on wellbeing may be via the direct effects in the brain where DHEA may act as a neurosteroid (2). Some population studies, however, have demonstrated a higher prevalence of major depressive disorders in women with high prohormone and androgen levels such as those with polycystic ovarian syndrome or congenital adrenal hyperplasia (42). A recent analysis of androgen precursors and androgen levels in 1659 women with mood disorders found no correlation of onset, remission, or recurrence of depression with androgen or sex hormone–binding globulin levels (43). However, many earlier studies examined giving DHEA for mood disorders. A recent meta-analysis of all studies where DHEA was administered for depression concluded that there may be a minor effect of DHEA administration; however, all the evidence was of low quality and thus it would be difficult to support the use of DHEA therapy to women with depression (44).

Metabolic bone health

Administration of DHEA in older adults was shown to have a sex-specific effect on bone mineral density (45, 46). Many of the small studies where DHEA was administered for wellbeing or other targets across the lifespan found variable effects on bone quality and density (47). Jankowski and coworkers examined pooled data from 295 women and 290 men aged 55 or older given DHEA or placebo for 12 months (45). Women showed increases in DHEAS, testosterone estradiol, and insulin-like growth factor 1, whereas men showed increases in DHEAS, estradiol and insulin-like growth factor 1. Women demonstrated a small increase in lumbar spine bone mineral density (1.0 ± 3.4%) and trochanter (0.5 ± 3.8%) and maintained total hip, whereas men showed no benefit on bone but a decrease in fat mass (45). This group and others examining effects in women with anorexia supported the conclusion that any bone effect of DHEA is via effects on changes in estrogen (36, 37, 46). Importantly, the effect size for DHEA therapy on the bone in women was significantly less than estrogen therapy or FDA-approved osteoporosis medications. No data are available concerning effects of DHEA supplementation on fracture risk.

Metabolic effects

Pharmacologic dosing of 100 mg daily demonstrated a decrease in fat mass and increase in strength in men, but not women (48). Decreases in serum leptin, but no effect on fasting glucose insulin, were observed; the authors concluded no significant effect on carbohydrate metabolism body composition or exercise capacity, and this is supported by others (48, 49). More recently, Nair and coworkers examined a 2-year intervention with DHEA 50 mg daily and showed no effects on body composition or peak volume of oxygen consumed per minute, muscle strength, or insulin sensitivity (19). Based upon data suggesting DHEA may act centrally on PPARα receptors related to fat oxidation and fat deposition (50), Villareal and Holloszy asked whether DHEA therapy would alter body composition as assessed using magnetic resonance imaging, a more sensitive measure (51). Twenty-eight women aged 71 (65-78) were assigned to receive DHEA 50 mg for 6 months. Similar to other reports in the literature, both testosterone and estradiol levels increased in the experimental group. DHEA supplementation decreased bodyweight (~0.9 compared with placebo +0.6 kg), associated with a decrease in visceral fat mass (10.2%) and subcutaneous fat (6%). They observed lower insulin levels and unchanged glucose, resulting in an increase in the insulin sensitivity index. The authors suggest an improvement in the risk or severity of metabolic syndrome associated with abdominal obesity. Although intriguing, the authors admit the changes observed after DHEA supplementation may be related to changes in estrogen after DHEA supplementation in women, and thus the risk/benefit of long-term administration would need to be considered.

Genitourinary symptoms

Genitourinary syndrome of the menopause affects 27% to 84% of postmenopausal women and can significantly impair health, sexual function, and quality of life (52). Initial interest in the use of DHEA for vaginal dryness was proposed by Labrie et al in 1997 when he administered a 10% DHEA cream to 14 women aged 60-70 and noted a vaginal estrogenic effect on the maturation index but no adverse effects on the atrophic endometrium (53). However, no measurements of DHEAs or other hormones were included. This observation started the interest in the safety and efficacy of synthetic DHEA, prasterone, for potential benefit with hypothesized fewer androgenic or estrogenic effects. Labrie and coworkers demonstrated the effectiveness of DHEA 0.50%, 6.5 mg of prasterone, on symptoms and signs of vaginal dryness (54). The question clinically, however, is whether DHEA is better or safer than nonhormonal therapies or low-dose topical or systemic estrogen therapy (55). Recent guidelines suggest initial use of nonhormonal agents such as vaginal lubricants and moisturizers, and then if not effective consideration of low-dose topical estrogen, DHEA, or the mixed agonist/antagonist ospemifene (56). No large head-to-head studies have been performed. Long-term studies on the endometrial safety of vaginal estrogen, vaginal DHEA, and ospemifene are lacking.

Infertility

Investigators have examined the potential role of administering testosterone or DHEA to women with unexplained infertility or decreased ovarian reserve with the hypothesis
that increase in androgens locally may improve ovarian function and fertility. DHEA is reported to be currently used in 25% of in vitro fertilization clinics without evidence of clear benefit. DHEA was administered in observational studies at a dose of 50 mg daily to women with diminished ovarian reserve and premature ovarian insufficiency with some success (57). These studies, however, were performed without control groups and thus cannot be recommended. Two recent meta-analysis showed conflicting conclusions concerning whether DHEA improved ovarian response in women with diminished ovarian reserve (58, 59). Studies with a placebo-controlled arm showed no benefit.

Adverse Effects of DHEA Administration to Women
Many trials did not provide data on adverse events. Of those that did, androgenic side effects (acne and hirsutism) appeared to be more common with DHEA than placebo, depending on the dose administered and targeted DHEA levels. Side effects were seen in women with adrenal insufficiency, ACTH deficiency, or anorexia. Similar results were reported in a meta-analysis of 28 trials of DHEA therapy in symptomatic postmenopausal women (38). DHEA did not improve quality of life, menopausal symptoms, or sexual function, but did increase androgenic side effects (acne and hirsutism) when compared with placebo or no treatment. Importantly, our patients need to understand that DHEA is metabolized to testosterone and estradiol, and administration would be contraindicated in women with a history of breast cancer or elderly women regarding the risk of estrogens in the cardiovascular system.

Abuse of Androgen Prohormones
Although abuse of androgen prohormones and testosterone have been detailed in men, less is known about the profiles in women athletes using pharmacologic doses of DHEA or other prohormones like androstenedione. Buisson and coworkers administered DHEA at 100 mg daily and detected a specific signature that would alert the authorities in the antidoping evaluation for female athletes. Concentrations of the urinary parameters of the steroid profile were highly impacted by short-term DHEA administration including the androgen epitestosterone (60). The most impacted markers in women were testosterone/epitestosterone and 5α-androstanediol/estradiol, with a detection window of 36 hours for 5α-androstanediol/estradiol. Thus, excess intake of DHEA or androstenedione would be readily detected if taken by athletes.

Novel Research Area for DHEA Administration
With the knowledge that after trauma there is an influx of inflammatory and immune reactions with elevated cortisol in relation to DHEAS levels, Bentley and coworkers have embarked on a prospective, phase II, single-center, cross-sectional, randomized study of DHEA in trauma patients (61). A dose-finding study is underway with sublingual or oral DHEA at 50 to 200 mg for 3 days after trauma. Women aged >50 with femur neck fracture and male and female patients with major trauma aged 16-50 will be recruited. Whether short-term DHEA administration will combat the high cortisol response after trauma is an intriguing question, or conversely whether this dichotomous divergence high cortisol/DHEA that is also observed in anorexia (35) and after injury is somehow protective and should not be altered. We await the results of this and future studies.

Conclusions
Back to our patient. This woman has primary adrenal insufficiency and has concomitant low adrenal prohormone levels. There are conflicting data in the literature concerning the benefit of DHEA in women with adrenal insufficiency at any age. In the premenopausal ages in women with low DHEAS levels, one could argue a trial of DHEA for potential benefits on wellbeing, understanding that the physiologic dose of DHEA in women is somewhere around 25 and not 50 mg/day. In the postmenopausal ages, one must consider the additional impact of conversion to testosterone and estradiol to her breast and bone health and cardiac risks, and discuss the pros and cons of a short-term trial. Long-term supplementation is not well established.

Since the last review of DHEA administration to women published by Davis in the Journal of Clinical Endocrinology & Metabolism in 2011 (47) and subsequent meta-analysis in 2014 (38), there are new studies and no new substantive data to argue for a re-examination of its use. Yet our patients looking for a panacea for all of their symptoms and deluged with suggestions for prohormones and other supplementation should be educated on the dose levels and potential risks. The next studies will help us determine whether the addition of the DHEA arm showed no benefit.

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Data Availability
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