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Long-Term Administration of Intravaginal Dehydroepiandrosterone on Regression of Low-Grade Cervical Dysplasia – A Pilot Study

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Key Words

Chemoprevention · Dehydroepiandrosterone · Neoplasia · Preinvasive cervical disease · Cervix · Dysplasia

Abstract

Although many dysplastic cervical lesions regress spontaneously, treatment is common due to concern for progression. Lesions persist or progress in women whose immune systems are unable to clear infection by human papillomavirus (HPV). Dehydroepiandrosterone (DHEA) is an adrenal steroid that has both immune modulatory and tumor inhibitory activity. A pilot study was conducted to examine the feasibility, safety and potential efficacy of intravaginal DHEA in women with low-grade cervical dysplasia. Twelve women with low-grade dysplasia, confirmed by colposcopic exam, were given 150 mg of intravaginal micronized DHEA daily for up to 6 months. Follow-up evaluations of the cervix were done at 3 and 6 months of use. DHEA, DHEA-S, androstenedione and testosterone levels were also measured. By the end of the study period, 10 of the 12 women (83%) had no evidence of dysplasia; the remaining 2 had normal colposcopic exams but cytology showing atypical cells of undetermined significance. There were no serious side effects. Androstenedione levels were elevated at 3 months, whereas testosterone levels were unchanged over the course of treatment. The results suggest that intravaginal DHEA is safe and well tolerated and may promote regression of low-grade cervical lesions. Further study is needed to establish efficacy.

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Introduction

With the increase in Pap smear screening, industrialized nations have seen a dramatic decrease in the incidence of cervical carcinoma. However, the incidence of low-grade cervical intraepithelial neoplasia has proportionally increased, with an estimated 2.5 million women diagnosed annually in the USA [1]. The management of patients with low-grade cervical disease is currently an area of controversy. Prospective and retrospective studies demonstrate a 60% spontaneous regression rate of these low-grade lesions without treatment, with 30% persisting as low-grade dysplasia and 10% progressing to more severe dysplasia and rarely, carcinoma [2]. When follow-up can be assured, current guidelines advocate managing

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these patients with repeat Pap smears at regular intervals. Treatment is indicated if progression of disease occurs, or if the low-grade disease persists. In practice, however, women with low-grade dysplasia frequently receive treatment with ablation or excision because of the inability to predict whose disease will progress.

In dysplastic cervical lesions, there is an increased rate of cell division with a proliferative expansion of abnormal basal epithelial cells. Over time, these cells can become transformed into malignant cells leading to cervical cancer. The role of human papillomavirus (HPV) as the etiologic agent in this process is now well established. However, the factors determining subsequent resolution or progression of early dysplastic lesions are not well understood, although it is clear from epidemiologic data that the immune system plays a critical role. Recognition of the importance of immune function in the progression to malignancy has led to the designation of cervical cancer as an AIDS-defining diagnosis, with the relative risk of developing invasive cervical cancer among HIV-positive women being proportional to the degree of immunosuppression [3]. Even in the absence of immunosuppression, recent studies have confirmed that cervical dysplasia develops in those individuals whose immune systems are unable to clear HPV, resulting in persistent infection [4, 5]. Among cigarette smokers, a decrease in the numbers of Langerhans' cells and CD4 cells in cervical stroma was demonstrated [6, 7], suggesting that the increased risk of dysplasia seen in association with tobacco use may be due, at least in part, from local immune suppression. The regression of early dysplasia, therefore, appears to depend on the ability of the immune system to eradicate virally infected hyperproliferative cells. The specific immune functions involved and whether they represent targets for prevention or treatment remains unclear.

Identification of a chemopreventive agent for preinvasive cervical disease would have a significant impact both through reduction of morbidity from invasive treatment as well as cost, currently estimated between USD 1.6 and 6 billion annually [8, 9]. A substance with potential chemopreventive action which has attracted recent attention is dehydroepiandrosterone (DHEA). In the second publication of Clinical Development Plans from the National Cancer Institute, Division of Cancer Prevention and Control, DHEA was identified as one of 16 promising chemopreventive agents deserving further study [10]. DHEA is an adrenal steroid whose levels decline with age and whose physiologic role is incompletely understood, although it appears to oppose many of the immunosuppressive effects of cortisol [11]. Interest in DHEA has grown because of reports finding potentially beneficial effects of the hormone on immune function and tumor inhibition. In mice, injection of DHEA resulted in significant epithelial protection against lethal herpes virus type 2 encephalitis and systemic coxsackievirus B4 infection [12]. Experiments using a mouse two-stage skin tumorigenesis model demonstrated that topical DHEA treatment inhibits tumor initiation as well as tumor promoter-induced epidermal hyperplasia and promotion of papillomas [13]. Additional studies have shown DHEA to inhibit in vivo growth of spontaneous mammary cancers [14], chemically induced cancers of the lung [15] and colon [16], as well as in vitro growth of thyroid [17], liver [18], human pancreatic [19], and melanoma cell lines [20]. In a rat chemical carcinogenesis model, both early and delayed DHEA administration resulted in significant protection against prostate carcinogenesis, suggesting it can suppress the progression of existing preneoplastic lesions to invasive disease [21].

Despite these promising findings, there have been no published studies examining the use of DHEA as a chemopreventive agent in humans. This may be due to the difficulty in finding a setting in which to study the potential immune-enhancing and anti-tumor activities of DHEA. Preinvasive cervical disease provides a unique opportunity as it is a lesion in which abnormal cell growth is the cardinal feature, and whose outcome, as a virally mediated disease, is likely to depend on cell-mediated immune function. We therefore sought to investigate whether DHEA promotes regression of preinvasive cervical disease. Vaginal administration was chosen because of the potential for higher local concentrations at the cervix. Although one previous published study had shown that DHEA was well absorbed and tolerated when given as a 150-mg vaginal tablet, the study involved single dosing of DHEA and did not address the tolerability of long-term use [22]. Therefore, since long-term dosing had not been previously studied, a pilot study was conducted to first assess the safety and feasibility of intravaginal DHEA administration in women with low-grade cervical dysplasia.

Methods

The study was opened after Food and Drug Administration requirements regarding the manufacture and quality control of the DHEA formulation were satisfied and the investigative protocol was approved by the Dana Farber/Partners Cancer Center Institutional Review Board, and the Mallinckrodt General Clinical Research Center at the Massachusetts General Hospital. Women receiving care at

the Gillette Women's Cancer Center at the Massachusetts General Hospital for whom cervical cytology demonstrated a low-grade squamous intraepithelial lesion, according to the Bethesda system criteria, underwent colposcopic exam and indicated biopsies and/or endocervical curettage. If the results of the colposcopic exam and histology were also consistent with low-grade dysplasia, patients were offered entry into the study. The length of the study period was 6 months. Patients were excluded for the following reasons: pregnant or actively desiring pregnancy, severe co-morbid illness, active hepatic dysfunction or active psychiatric illness, history of AIDS, status post solid organ transplant or bone marrow transplant, presence of concomitant high-grade cervicovaginal dysplasia, or inability for reliable follow-up. The current management of patients with low-grade cervical dysplasia in these clinics is repeat Pap smear and colposcopy with biopsies and/or endocervical curettage as indicated, every 3–4 months for 1 year, with treatment if disease is persistent or if progression to more severe dysplasia occurs. This follow-up protocol was not altered by participation in the study.

After informed consent was obtained, patients were given a 1-week supply of DHEA tablets with instructions to place one tablet high in the vagina at bedtime daily. DHEA was provided to patients as 150-mg pharmacopoeia-grade vaginal micronized tablets. Patients were instructed not to use other vaginal medications or oral DHEA formulations while participating in the study. Initial baseline laboratory tests at study entry included urine pregnancy test, SGOT, DHEA, androstenedione and testosterone. Follow-up blood testing for DHEA levels was performed 1 week after starting the medication at which time patients were given a 3-month supply of pills. Patients were then followed as they would be under standard care for their cervical disease, returning at 3- and 6-month intervals for repeat Pap smear and colposcopy. Biopsy and endocervical curettage were done at the time of the follow-up visit only if there was an indication based on findings at colposcopic exam. Repeat blood testing for SGOT, DHEA, androstenedione and testosterone levels were performed immediately following the 3- and 6-month visits. In addition, patients were given diaries in which to record pill use and side effects and instructed to call the study investigators with any unusual symptoms attributable to the DHEA use.

Statistical analyses of DHEA, DHEA-S, androstenedione and testosterone levels were done using the Student's t test for paired samples.

Results

Fourteen women were enrolled in the study; however, 2 women withdrew from the study before beginning any medication. The mean age of the 12 women who began using the intravaginal DHEA formulation was 30.6 years (range 20–44); all were premenopausal. Only 1 patient was a smoker. All women had a low-grade squamous intraepithelial lesion on cervical cytology and underwent colposcopy; the diagnosis was confirmed histologically for 9 of the 12 women by colposcopic directed biopsy and for 1 woman by endocervical curettage prior to enrollment. Two women had the diagnosis based on cervical cytology and colposcopy alone.

All 12 women who began the medication continued through the 3-month visit. Seven patients continued for the full 6 months of treatment. Although none of the patients reported difficulty in self-administration, the daily dosing and length of time of treatment were anticipated to be the main obstacles to compliance. Patients were questioned regarding compliance at each visit. No patient reported lapses in self-administration of more than 2 days. There were no reports of vaginal discomfort or abnormal discharge although some patients noted pill fragments up to 6 h after application. Two patients withdrew from the study due to attributed side effects of the medication. One patient reported symptoms of dysuria at 3 months and 1 complained of acne, which she noted at approximately 4 months of therapy. The patient with dysuria had not had any previous episodes of dysuria during DHEA use and did not complain of symptoms of vaginal irritation or discharge. Her urinalysis was normal and the symptom rapidly resolved without treatment. Both of these patients had had apparent regression of disease at the 3-month visit and both elected to discontinue the study when the symptoms appeared. There were no serious adverse events in the study. Liver function as measured by SGOT remained normal in all patients except 1, who had a transient increase in SGOT to 88 at the 3-month visit (institutional upper limit of normal = 25). Repeat SGOT testing was normal and the patient continued the study with a subsequently normal SGOT at 6 months. Despite the fact that patients were counseled not to become pregnant during the study, 2 patients became pregnant and were withdrawn from the study. Both patients had reported condoms as their method of birth control. One patient moved from the study area after 3 months.

DHEA levels were available for 12 patients for the baseline and 1-week values, for 9 patients at 3 months and for 5 patients at 6 months. For the available values, DHEA levels increased significantly over baseline at 1 week and 3 months, but not at 6 months ($p = 0.004$, 0.004 and 0.43 respectively). For the same time intervals, DHEA-S levels were available for 12, 10, 11 and 5 patients respectively. DHEA-S levels were significantly elevated over baseline at 1 week but not subsequently. Testosterone levels were available for comparison at baseline and 3 months for 9 patients, and at 6 months for 6 patients. There was no statistically significant increase in testosterone levels from baseline seen at either 3 or 6 months ($p = 0.36$, $p = 0.17$). Androstenedione levels were significantly elevated compared to baseline at 3 months ($p = 0.006$), but not at 6 months ($p = 0.09$) (fig. 1a–d).

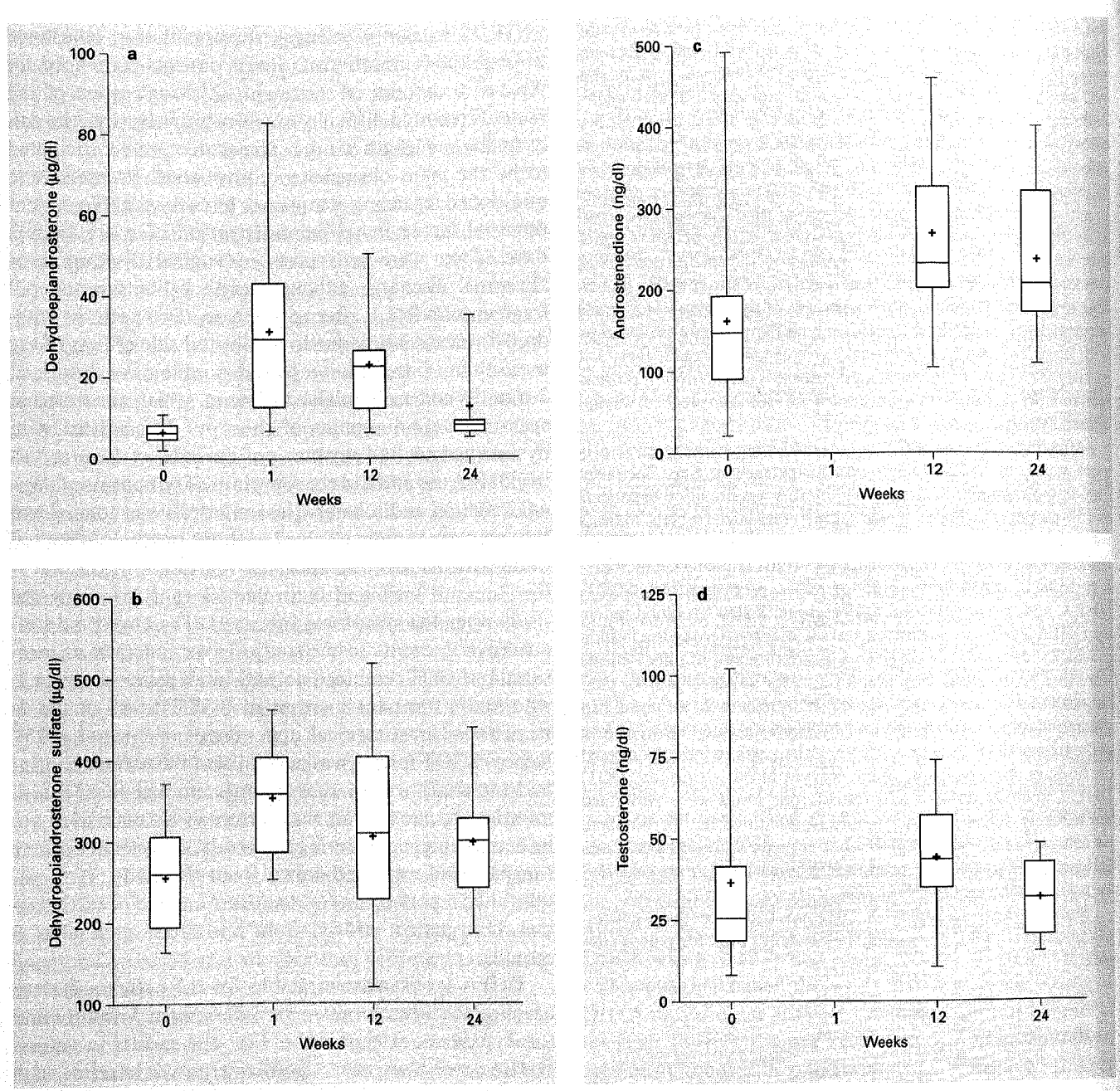

Fig. 1a–d. Box plots showing change in serum levels of **a** dehydroepiandrosterone (DHEA), **b** dehydroepiandrosterone sulfate (DHEA-S), **c** androstenedione and **d** testosterone during intravaginal administration of DHEA in women with low-grade cervical dysplasia.

Twelve patients took the drug for at least 3 months and returned for follow-up examination. Of the 12 patients evaluated, 10 (83%) had apparent regression of disease with no evidence of dysplasia on follow-up during the study period (table 1). Seven of these had regression at the 3-month exam; 3 had regression at 6 months. The patient who smoked cigarettes during the study was included in the group who regressed at 6 months. There were no patients who had normal examinations at 3 months who had recurrent dysplasia at 6 months. The remaining 2

Table 1. Results of 3- and 6-month follow-up colposcopic evaluation, Pap smear, indicated biopsies and/or endocervical curettage (ECC) for women with low-grade cervical dysplasia (LGSIL) using intravaginal dehydroepiandrosterone (DHEA)

Patient	Baseline	3-Month evaluation	6-Month evaluation
1	Pap: LGSIL	Biopsy: LGSIL Negative ECC	Negative biopsy ×2 Negative ECC Negative Pap
2	Pap: LGSIL Biopsy: LGSIL	Negative ECC Negative Pap	Negative ECC Negative Pap
3	Pap: LGSIL Biopsy: LGSIL	Pap: 'ASCUS favor reactive' Negative biopsy Negative ECC	Off study
4	Pap: LGSIL Biopsy: LGSIL	Pap: 'rare cells showing mild dysplasia' Negative biopsy Negative ECC	Negative biopsy ×2 Negative Pap
5	Pap: LGSIL Biopsy: LGSIL	Negative Pap Negative ECC	Off study
6	Pap: LGSIL Biopsy ×2: LGSIL	Negative biopsy ×2 Negative ECC Negative Pap	Negative biopsy Negative ECC
7	Pap: LGSIL Biopsy: LGSIL	Pap: ASCUS Negative colposcopy	Off study
8	Pap: LGSIL Biopsy: LGSIL	Pap: ASCUS Negative colposcopy	Negative Pap Negative colposcopy
9	Pap: LGSIL ECC: LGSIL	Negative Pap Negative ECC	Off study
10	Pap: LGSIL	Negative Pap Negative biopsy	Negative Pap Negative colposcopy
11	Pap: LGSIL Biopsy: LGSIL	Pap: ASCUS Negative colposcopy	Negative Pap Negative colposcopy
12	Pap: LGSIL Biopsy ×2: LGSIL	Negative Pap Negative biopsy	Off study

ASCUS = Atypical squamous cells of undetermined significance.

patients had normal colposcopicexaminations at the end of the study period, but cytologic smears showing atypical squamous cells of undetermined significance (ASCUS).

Discussion

The mechanism by which DHEA inhibits tumor growth is unknown. However, DHEA levels appear to be strongly correlated with levels of immune cytokines. In a recent study examining the correlation between sex hormones and cytokine secretion in vivo, levels of DHEA-S in premenopausal women were highly correlated with activity of interferon-γ-secreting cells [23]. In mouse models, DHEA has been found to have a direct affect on cytokine production. Mice injected with DHEA had significant increases in serum levels of interleukin (IL)-10, a potent differentiation factor of B lymphocytes [24]. IL-10 has also been shown to potentiate cytotoxic activity of HPV E7-specific CD8+ T lymphocytes in vivo [25]. Since it was observed that the age-related decline in DHEA levels mirrors decreases in certain aspects of immune func-

tion, initial human studies using DHEA were done in elderly populations to investigate whether a significant relationship exists. Oral DHEA (50 mg/day) was associated with enhanced natural killer cell cytotoxicity and number and higher levels of IL-2 secretion from activated T lymphocytes in postmenopausal women [26–28], and significant increases in several indices of immune function in elderly males [29]. Depressed DHEA levels seen in HIV disease have been correlated with cytokine dysregulation [30]. At the molecular level, DHEA was found to inhibit mammary carcinogenesis induced by polycyclic aromatic hydrocarbons via an inhibition of carcinogen-activating enzyme cytochrome P_{450} 1A1 (CYP1A1) mRNA expression by a post-transcriptional mechanism [31].

The negative side effects of DHEA therapy have been related to increased androgen levels [32]. DHEA is metabolized in the liver and converted in peripheral tissues to androstenedione, dihydrotestosterone and testosterone. The only published long-term study used oral DHEA 200 mg/day for 3 months in premenopausal women with the only adverse side effect being increased acne, noted in 47% of individuals receiving DHEA [33]. In this double-blind prospective clinical trial of systemic lupus patients, a significant decrease in the number of lupus flares were seen in the DHEA group, with acne being the only adverse effect. As the androgenic effects of DHEA stem from the metabolism of DHEA, vaginal administration of the drug which avoids the portal circulation and thereby modifies hepatic first-pass metabolism was chosen for use in this study. A previous randomized study compared 150 mg of vaginal micronized DHEA with oral DHEA and found that after single-dose vaginal administration, equivalent serum DHEA levels of approximately twice the baseline values were achieved without significant increases in DHEA-S or testosterone [22]. In this study, androstenedione but not testosterone levels were significantly higher during DHEA use. Acne was reported by only 1 patient and was noted after 4 months of use.

The study was aimed primarily at assessing the tolerability and potential side effects of long-term intravaginal DHEA use; the number of patients studied does not provide sufficient power to draw definite conclusions regarding efficacy. Nevertheless, of the 12 women treated, 10 (83%) had complete regression of dysplasia by colposcopic exam, Pap smear and indicated biopsies and/or endocervical curettage, with the remaining 2 patients having ASCUS cytology only. Regression rates for low-grade dysplasia have been reported between 40 and 70% [35, 36]; however, these rates are cumulative over 2–5 years of observation. The expected regression rate at 3 and 6 months may be lower. Although the inherent variability in diagnosing and categorizing dysplasia may have influenced the results, we specifically did not require confirmatory biopsies on patients under treatment, since the primary purpose of the study was to evaluate the acceptability of the regimen in women whose care was otherwise unaltered from the standard follow-up surveillance for low-grade disease. Therefore, while these results are suggestive of a possible effect, further study in the form of a randomized controlled trial is needed to fully evaluate the activity of DHEA on regression of cervical dysplasia. The immune enhancing and anti-tumor activities of DHEA make it a promising potential therapeutic agent in the setting of preinvasive cervical disease. The results from this study suggest that long-term use of intravaginal DHEA is safe and well tolerated and may promote regression of low-grade cervical dysplasia.

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