Intravaginal dehydroepiandrosterone (prasterone), a highly efficient treatment of dyspareunia


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ABSTRACT

Objective To examine the effect of intravaginal dehydroepiandrosterone (DHEA) on pain at sexual activity (dyspareunia) identified as the most bothersome symptom of vaginal atrophy in postmenopausal women at both screening and day 1.

Methods This prospective, randomized, double-blind and placebo-controlled phase III clinical trial studied the effect of prasterone (DHEA) applied locally in the vagina on the severity of dyspareunia in 114 postmenopausal women who had identified dyspareunia as their most bothersome symptom of vaginal atrophy, while meeting the criteria for superficial cells ≤5% and pH > 5.0 at both screening and day 1.

Results At the standard duration of 12 weeks of treatment, increasing doses of 0.25%, 0.5% and 1.0% DHEA decreased the percentage of parabasal cells by 48.6 ± 6.78%, 42.4 ± 7.36% and 54.9 ± 6.60% (p < 0.0001 vs. placebo for all) with no change with placebo (p = 0.769). The effects on superficial cells and pH were also highly significant compared to placebo at all DHEA doses. The severity score of pain at sexual activity decreased by 0.5, 1.4, 1.6 and 1.4 units in the placebo and 0.25%, 0.5% and 1.0% DHEA groups, respectively, with the p value of differences from placebo ranging from 0.0017 to < 0.0001.

Conclusions Intravaginal DHEA, through local estrogen and androgen formation, causes a rapid and highly efficient effect on pain at sexual activity without systemic exposure of the other tissues, thus avoiding the recently reported systemic effects of estrogens.

INTRODUCTION

Women now spend at least one-third of their lifetime during postmenopause, with the high probability of suffering from one or more of the problems related to hormone deficiency, namely vaginal atrophy, hot flushes, osteoporosis, muscle loss, fat accumulation, type 2 diabetes, memory loss, cognition loss and possibly Alzheimer’s disease. An estimated 60 million women are over 45 years of age in 2010 in the US1.

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Recently, a series of reports have indicated that systemic estrogens + progestins and estrogens alone increase the risk of breast\(^5\text{-}^9\), ovarian\(^9\text{-}^11\) as well as endometrial (estrogens alone)\(^12\text{-}^13\) cancer. The publicity that followed the publication of the data from the Women’s Health Initiative Study\(^11\) has led to the suggestion by the medical community to use the lowest estrogen dose possible for the minimal time duration in order to minimize risks.

In order to avoid the risks of estrogens, we have developed a novel approach to hormone deficiency after menopause that is based upon the recent progress achieved in our understanding of sex steroid physiology in women\(^14\text{-}^16\) and the recognition that women, at menopause, are not only deprived of estrogen activity due to an arrest of ovarian estrogen secretion, but have already been submitted for a few years to a decreasing exposure to androgens caused by declining dehydroepiandrosterone (DHEA) secretion by the adrenals\(^17\).

A very compelling demonstration of the efficacy and safety of DHEA has recently been obtained in a pivotal phase III, placebo-controlled, randomized clinical trial in which postmenopausal women suffering from vaginal atrophy received daily DHEA or placebo intravaginally for 12 weeks. 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\(^18\text{-}^20\). In order to meet the recent requirements of the Food and Drugs Administration (FDA) which indicate the choice of a single self-identified most bothersome symptom of vaginal atrophy at both screening and day 1 while meeting the criteria of superficial cells ≤5% and pH > 5.0, we have analyzed the data obtained in women who met these slightly revised guidelines.

**METHODS**

This study is a phase III, prospective, multicenter, randomized, placebo-controlled and double-blind trial. The original intend-to-treat (ITT) population included 216 postmenopausal women randomized to receive a daily intravaginal ovule of the following DHEA concentrations: 0.0% (53 women), 0.25% (3.25 mg DHEA, 53 women), 0.5% (6.5 mg DHEA, 56 women) or 1.0% (13 mg DHEA, 54 women) administered intravaginally with an applicator at bedtime for 12 weeks\(^18\). From this total population, 114 women self-identified pain at sexual activity (dyspareunia) as their most bothersome symptom at both screening and day 1, while meeting the criteria for superficial cells ≤5% and pH > 5.0, thus meeting the revised FDA guidelines.

The DHEA ovules or suppositories (Vaginorm\(^\text{TM}\)) containing prasterone in a lipophilic base were manufactured by Recipharm, Karlskoga, Sweden. The study was divided into two phases, namely screening followed by a treatment period of 12 weeks. The protocol was approved by the Institutional Review Board of the Centre Hospitalier de l’Université Laval (Quebec City, Canada), McGill University (Montreal, Canada), Ethica (Montreal, Canada), Eastern Virginia Medical School (Norfolk, Virginia, USA) and the Western Institutional Review Board (Los Angeles, USA).

The inclusion and exclusion criteria were as described by Labrie and colleagues in reference 18.

A written informed consent was obtained from all subjects prior to the performance of any study-related procedure. The subjects had a medical history, a medical examination and a complete gynecological examination at screening. A partial gynecological examination was performed to evaluate the aspect of the mucosa and tolerance to the medication on day 1 and at all visits.

The standard laboratory tests, namely hematology (including complete blood count and coagulation), blood chemistry and urinalysis, were performed at screening, day 1 and at all visits.

Vaginal cell smears and endometrial biopsies were examined in a central laboratory. A 100-cell count was performed to classify cells as superficial, intermediate or parabasal squamous cell types\(^21\text{-}^22\). Vaginal pH was measured by applying a pH indicator strip directly to the lateral wall of the vagina with a forceps.

The women included in the present analysis identified dyspareunia as the most bothersome symptom at the start of treatment (both screening and day 1) while having ≤5% of superficial cells in the vaginal smear and a pH > 5.0. The change in severity of dyspareunia was followed and served to evaluate the effect of treatment in addition to changes in vaginal cell maturation and pH. The severity of dyspareunia was classified by women as being none, mild, moderate or severe and was analyzed using corresponding values of 0, 1, 2 or 3, respectively, as originally described\(^18\). All endpoints had to demonstrate statistically significant effects relative to placebo. The primary time-point for analysis was the 12-week assessment. Statistics were performed as described\(^18\).

**RESULTS**

When the statistical analysis was made for patients from the ITT population who had moderate to severe dyspareunia as their most bothersome symptom and also met the superficial cells and pH criteria (superficial cells ≤5% and pH > 5.0) at both screening and day 1 (baseline), 26, 29, 30 and 29 patients were eligible in the placebo and 0.25%, 0.5% and 1.0% DHEA groups, respectively.

As illustrated in Figure 1, at the standard duration of 12 weeks of treatment, increasing doses of 0.25%, 0.5% and 1.0% DHEA decreased the percentage of parabasal cells by 68.6 ± 6.78% (from 65.5 ± 6.92% to 16.9 ± 3.66%; p < 0.0001), 42.4 ± 3.66% (from 53.4 ± 7.49% to 11.0 ± 3.43%; p < 0.0001) and 54.9 ± 6.60% (from 61.8 ± 6.88% to 6.9 ± 1.77%; p < 0.0001), respectively, while no significant effect was observed in the placebo group (from 46.7 ± 8.64% to 47.8 ± 7.52%; p = 0.7686). It can be
seen in the same figure that all doses of DHEA are highly significantly different from placebo (\(p < 0.0001\) for all).

While no significant change was seen at 12 weeks in the placebo group compared to baseline in the percentage of superficial cells (Figure 2), increases of 5.3 ± 1.39% (from 0.4 ± 0.15% to 5.7 ± 1.33%; \(p = 0.0006\)), 4.8 ± 1.20% (from 0.4 ± 0.11% to 5.2 ± 1.19%; \(p = 0.0004\)) and 6.1 ± 1.54% (from 0.4 ± 0.16% to 6.5 ± 1.53%; \(p = 0.0005\)) were measured in the 0.25%, 0.5% and 1.0% DHEA groups, respectively. It can be seen in the same figure that the differences from placebo had respective \(p\) values of 0.0052, 0.0111 and 0.0012 for the three increasing doses of DHEA, respectively.

Vaginal pH, on the other hand, was decreased at 12 weeks by 1.1 ± 0.16 pH units (\(p < 0.0001\); from 6.6 ± 0.10 to 5.5 ± 0.19 units), 1.5 ± 0.18 pH units (\(p < 0.0001\); from 6.6 ± 0.09 to 5.2 ± 0.17 units) and 1.4 ± 0.15 pH units (\(p < 0.0001\); from 6.5 ± 0.11 to 5.1 ± 0.12 units) in the 0.25%, 0.5% and 1.0% DHEA-treated groups, respectively. As indicated in Figure 3, all doses of DHEA are highly significantly different from placebo with \(p\) values of 0.0127, 0.0001 and 0.0001 for the three increasing doses of DHEA, respectively.

At the 12-week interval, the severity score of the most bothersome symptom identified at baseline as dyspareunia was reduced from 2.8 ± 0.08 to 2.3 ± 0.18 (\(p = 0.0132\)), from 2.8 ± 0.08 to 1.4 ± 0.22 (\(p < 0.0001\)), from 2.7 ± 0.08 to 1.1 ± 0.22 (\(p < 0.0001\)) and from 2.6 ± 0.09 to 1.2 ± 0.20 (\(p < 0.0001\)) in the placebo and increasing DHEA dose groups, respectively (Figure 4). It can be seen in the same figure that the differences from placebo had respective \(p\) values of 0.0017, < 0.0001 and 0.0003 for the three increasing doses of DHEA, respectively.

Concerning safety, no drug-related significant adverse event was observed in the present study nor in our previous 1-week pharmacokinetics study with doses of 0.5%, 1.0% and 1.8% DHEA ovules\(^{23,24}\). No adverse effect was observed on hepatic tests, hematocrit or any hematological or biochemical parameter.

**DISCUSSION**

The present data clearly demonstrate the high efficacy of intravaginal DHEA on pain at sexual activity, the most frequently vaginal atrophy symptom self-identified by women in our recent study\(^{18,19}\). In that previous analysis on the ITT population where 129 women out of 216 had identified dyspareunia as their most bothersome symptom, the 0.25%, 0.5% and 1.0% doses of DHEA caused 50% (\(p = 0.0009\) vs. placebo), 60% (\(p < 0.0001\) vs. placebo) and 58% (\(p < 0.0001\) vs. placebo) decreases in the severity of dyspareunia. The effect was already significant at 8, 8, and 2 weeks for the 0.25%, 0.5% and 1.0% DHEA doses, respectively\(^{18}\).

The present analysis shows that almost super-imposable effects are observed when the entry criteria (pain at sexual activity as most bothersome symptom, superficial cells ≤ 5% and pH > 5.0) are met at both screening and day 1. In fact,
using the ITT population meeting the entry criteria at both screening and day 1, the 0.25%, 0.5% and 1.0% doses of DHEA caused 50% (p < 0.0017 vs. placebo), 59% (p < 0.0001 vs. placebo) and 54% (p = 0.0003 vs. placebo) decreases in the severity score of pain at sexual activity at 12 weeks of treatment.
Current treatments of vaginal atrophy include systemic hormone therapy, intravaginal estrogens and non-hormonal lubricants and moisturizers\textsuperscript{25,26}. The risks of estrogens mentioned above have led to the development of lower doses of intravaginal estrogens\textsuperscript{27,28}, although serum estrogens are still increased above normal postmenopausal values with these low-dose regimens\textsuperscript{29}.

Another approach has been to use ospemifene, a mixed estrogenic/antiestrogenic SERM (selective estrogen receptor modulator)\textsuperscript{30}. Ospemifene is a first-generation SERM, a close analog of tamoxifen and toremifene, with comparable estrogenic/antiestrogenic relative activities\textsuperscript{31}. Accordingly, ospemifene has been shown to stimulate uterine weight and endometrial thickness in the rat\textsuperscript{31,32}. In agreement with its intrinsic estrogenic activity exposing all tissues following its systemic administration, ospemifene, in a large scale 12-week classical study on vaginal atrophy, has shown beneficial effects on vaginal cell maturation and pH\textsuperscript{30}. Concerning dyspareunia, the daily 30 mg dose of ospemifene did not have a statistically significant effect compared to placebo on the severity score (1.02 unit change compared to 0.89 in the placebo group for a difference of 0.13 unit), while the 0.3 unit decrease over placebo in the severity score of dyspareunia observed with the daily 60 mg dose of ospemifene reached significance with an improvement of 0.3 unit in the severity score ($p = 0.023$)\textsuperscript{30}.

By comparison, with the lowest dose (0.25%, 3.25 mg) of daily intravaginal DHEA, the decrease in the severity score of dyspareunia was 0.9 units over placebo with a $p$ value of 0.0017. At the 0.5% DHEA dose, the decrease in the severity score of dyspareunia over the placebo effect was 1.1 units ($p < 0.0001$) compared to only 0.3 units for ospemifene 60 mg ($p = 0.023$) and 0.13 units for ospemifene 30 mg (not significant). In fact, at the lowest dose of DHEA used (0.25%, 3.25 mg per day), the decrease in the severity score of dyspareunia was 6.9 times higher (0.9 vs. 0.13 units) than the non-significant effect observed with the 30 mg dose of ospemifene, while it was three times more efficient than the 60 mg daily dose of ospemifene. With the 0.5% DHEA dose (6.5 mg daily), the effect on dyspareunia was 8.5 (1.1 vs. 0.13) and 3.7 (1.1 vs. 0.3) times more important than the 30 and 60 mg doses of ospemifene, respectively. Since the lubricant was used only in 31%, 22% and 29% of women in the ospemifene 30 and 60 mg and placebo groups, respectively, during the last week of treatment and in about one-third at the beginning, the difference cannot reasonably be explained by the placebo effect of the lubricant not used in two-thirds of women.

Although 75% of postmenopausal women suffer from vaginal atrophy\textsuperscript{33,34}, thus affecting their quality of life during a major part of their lifetime, only 20% or less seek treatment\textsuperscript{35}. The fear of breast cancer associated with the prescription of estrogens is the main reason for the lack of acceptance of estrogen therapy by most women and their physicians. In the aftermath of the Women’s Health Initiative study, the scientific challenge is to explore alternative types and formulations of hormone therapy that would provide all the menopausal advantages of estrogens while improving women’s quality of life, minimizing risks, and maximizing benefits\textsuperscript{36}.

The traditional concept of sex steroid physiology in women was based on the assumption that all estrogens were of ovarian origin. The relatively recent developments of mass spectrometry technology have permitted us to gain new and
crucial information in this field\textsuperscript{17–39}. In fact, the traditional concept does not apply to humans and is valid only for animal species lower than primates, where the ovaries are the only source of sex steroids.

Since, according to physiology, women are no longer exposed to systemic estrogens after menopause, it is reasonable to believe that the non-physiologic situation created by the administration of estrogens could be responsible for at least some of the side-effects reported by women receiving traditional estrogen and estrogen/progestin replacement therapy\textsuperscript{3,11,12,40–44}. These side-effects are in addition to the well-recognized stimulation of the endometrium by unopposed estrogens and the resulting endometrial hyperplasia and risk of carcinoma\textsuperscript{12,13}.

It is important to remember that a unique advantage of DHEA is that this compound is an inactive precursor or prodrug, which is transformed into active sex hormones (estrogens and/or androgens) only in the specific cells and tissues which possess the required enzymes. Due to the decreasing serum levels of DHEA with age, these tissues, however, are exposed to lower and lower levels of DHEA\textsuperscript{45,46}, thus progressively reducing the formation of sex steroids and causing symptoms in most, but not all, postmenopausal women. Based upon our data obtained with intravaginal DHEA\textsuperscript{18–20,23,24}, it is reasonable to believe that supplementation with DHEA in the symptomatic woman simply mimics the situation of the higher DHEA activity present in healthy asymptomatic women. Consequently, women with symptoms of vaginal atrophy and receiving DHEA should not be 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, where high doses of DHEA have been administered orally or percutaneously in a large series of women for up to 2 years (for review, see reference \textsuperscript{47}). 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 significant DHEA-related safety concerns.

Moreover, no significant adverse event related to DHEA was observed in a study performed in 75 women randomized to receive 3 g of 0.3\% DHEA percutaneously twice daily for 12 months\textsuperscript{39} or 15 women who received daily 3–5 g of 10\% DHEA cream for 1 year\textsuperscript{48}.

Persistent controversial data relate to the search for a potential correlation between desire and serum testosterone in healthy women\textsuperscript{49–51}. In fact, most studies have found no correlation between serum testosterone and arousal\textsuperscript{49}. It is important to indicate that this lack of correlation can be explained by the finding that serum testosterone is clearly not a valid parameter of androgenic activity in women\textsuperscript{37}.

Our recently published study\textsuperscript{19} has shown for the first time that local intravaginal treatment with DHEA causes a marked improvement in all four aspects of women’s sexual dysfunction, namely, desire/interest, arousal, orgasm, and pain at sexual activity. It thus seems that increased favorable sensitive outputs from a more healthy vaginal area influence the brain to feel increased desire/interest without the need for a direct action of hormones on the brain. The decrease in pain at sexual activity described above is likely to play a major role in improving sexual functions in postmenopausal women.

**Conflict of interest**

F. Labrie is President of EndoCeutics.

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