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Supplementation of dehydroepiandrosterone (DHEA) in pre- and postmenopausal women — position statement of expert panel of Polish Menopause and Andropause Society

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ABSTRACT

Dehydroepiandrosterone (DHEA) concentration decreases with age, therefore, DHEA has been considered a hormone that reduces the symptoms associated with aging, so the usefulness of DHEA in premenopausal and postmenopausal women, and the options of hormone therapy have received a large amount of attention. The effectiveness of DHEA in the premenopausal women remains unclear, while in postmenopausal women with coexisting estrogens deficiency is controversial. Despite many years of study, the use of DHEA is still controversial, especially regarding its effectiveness. The aim of present article was to evaluate DHEA specific effects on metabolic parameters, bone mineral density, insulin resistance as well as the therapeutic potential of DHEA in pre- and postmenopausal women using measures of sexual activity, cognition and well-being. The summary of this article is the position statement of expert group of the Polish Menopause and Andropause Society regarding the efficacy and safety of DHEA supplementation in women. We concluded, that currently available clinical trials and meta-analyses indicate that DHEA supplementation is effective in women with adrenal insufficiency and chronically treated with exogenous glucocorticoids, postmenopausal women with low bone mineral density and/or osteoporosis, premenopausal women with sexual disorders and low libido, and in women with vulvovaginal atrophy due to menopause or genitourinary syndrome of menopause. Currently available clinical trials also suggest that DHEA supplementation is probably effective in postmenopausal women with hypoactive sexual disorders, infertile women with diminished ovarian reserve, women suffering from depression and anxiety, and women with obesity and insulin resistance. No serious adverse effects have been reported.

Key words: dehydroepiandrosterone; perimenopause; menopause

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INTRODUCTION

Dehydroepiandrosterone (DHEA) represents the most abundant steroid hormone in humans. DHEA concentration gradually decreases with age reaching the lowest levels about the time when the incidence of many diseases increases. Therefore, DHEA has been considered a hormone that slows down or prevents aging, or at least reduces the symptoms associated with aging, therefore the usefulness of DHEA in perimenopausal and menopausal women, and the options to hormone therapy have received a large amount of attention.

However, not all aspects of physiology, pathophysiology, mechanism of actions, clinical relevance and safety of DHEA supplementation in women have been known to date. The effectiveness of DHEA in the premenopausal women remains unclear, while in postmenopausal women many symptoms are caused by both estrogens and DHEA deficiency. Therefore, it is difficult to clearly distinguish between menopause and adrenopause. Despite many years of study, the use of DHEA is still controversial, especially regarding its effectiveness.

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The aim of present article was to evaluate DHEA specific effects on metabolic parameters, bone mineral density, insulin resistance as well as the therapeutic potential of DHEA in pre- and postmenopausal females using measures of sexuality, cognition and well-being. The summary of this article is the position statement of expert group of the Polish Menopause and Andropause Society regarding the efficacy and safety of DHEA supplementation in women.

DHEA IN HUMAN PHYSIOLOGY

Dehydroepiandrosterone (DHEA) is an endogenous androgen produced in zona reticularis of adrenal cortex (30%), thecal cells in ovary (20%), and from peripheral conversion of DHEAS (30%).

In peripheral tissues DHEA is converted to more active androgens and estrogens: estrone and testosterone and later to estradiol and dihydrotestosterone (DHT) respectively. The contribution is remarkable, since in postmenopausal women 40–75% of testosterone and 90% of estrogens are derived from adrenal androgens [1]. DHEA-S serves as a circulating reservoir of DHEA. DHEA can be reversely transformed in many tissues by sulphatases from its sulphate (DHEA-S). Together with its sulphate, DHEA is the most concentrated hormone and the most abundant steroid in peripheral blood, thus it became clear that it is more than just an intermediate in steroid hormone synthesis. Serum DHEA concentrations range from 0.2 to 0.9 mcg/dL (7 to 31 nmol/L). Due to its remarkable and gradual decrease that occurs with aging, DHEA was considered as an anti-aging elixir and concept of dietary supplementation of DHEA was promoted and administration was introduced in 1980s [2]. As primary effects improvement in sexual function, well-being, metabolic parameters, immune response, and cognition were suggested. Noteworthy many initial studies regarding anti-aging properties and mechanisms of DHEA were conducted on rodents that naturally do not secrete DHEA from adrenal glands, thus may be irrelevant [3]. DHEA also plays an important role in reproductive endocrinology. As other androgens, DHEA is important in follicular steroidogenesis and oogenesis in ovary. Described effects on ovarian folliculogenesis includes upregulation of insulin-like growth factor-1 (IGF-1) [4], sensitization to gonadotropins and reduction of follicular arrest [5].

Secretion of DHEA is stimulated by ACTH from pituitary gland; however, levels of DHEA-S are not linked directly to ACTH due to long plasma half-life time and high concentration of the sulphate. The hydrophilic DHEA-S is secreted mainly by adrenal glands and is a major circulating and most stable form of DHEA that can easily be interconverted in target tissues. Metabolism of DHEA is modulated by binding to plasma proteins, since SHBG have low affinity to DHEA and no affinity to DHEA-S. Albumins weakly binds DHEA but have high affinity to DHEA-S and increases its half-life time [6].

Physiologically, their production clearly increases in children between 6–8 years of age, which is called adrenarche. These hormones in the child's target tissues are converted to steroids with more activity. The place of conversion is, inter alia, the skin. Pubic hair appears apocrine sweat glands begin to function, and sebaceous gland secretion increases. At this time, slight acceleration is also observed in bone growth and maturation. DHEA and DHEA-S levels have been shown to depend on nutritional status. Obese children have higher levels of DHEA-S and earlier achieve adrenarche than lean children. Some research suggests that adrenal androgens directly or after peripheral conversion to estrogen modulate hypothalamic activity influencing the gonadarche. DHEA and DHEA-S concentrations increase gradually to the third decades of life. Peak secretion of these hormones falls for ages between 20 and 30 years old. Levels since then DHEA and DHEA-S in the blood gradually decrease to reach 20% of its maximum value in its 70s, up to a fall to 5% at the age of 85–90 [7]. Humans and primates are unique in their capacity to produce large amounts of adrenal steroids.

In postmenopausal women ovarian production of DHEA is ceased in contrast to testosterone that is still produced by postmenopausal ovaries for many years [8]. Diverse conditions influence the DHEA(S) activity. DHEA and DHEA-S can be suppressed in many pathological conditions including acute stress, severe chronic systemic diseases, anorexia nervosa, ACTH-independent Cushing's syndrome and chronic medication with anti-inflammatory doses of glucocorticoids (GCS). Higher levels were described in hyperprolactinemia [3].

DHEA exerts its primary effects through its estrogenic and androgenic derivatives since a unique DHEA receptor is not known. However, DHEA exhibits a weak antagonist effect on the androgen receptor (AR) [9]. It was described that DHEA plays a role as a low-affinity ligand for hepatic nuclear receptors, such as the pregnant X receptor, the constitutive androstane receptor, and estrogen receptors α/β (ERα/ERβ) as well as G protein-coupled ER (GPER1) [1]. Moreover, DHEA may act in brain as an stimulatory neuromodulator by blocking the action of the gamma-aminobutyric acid type A (GABA) receptor, as well as, activating the N-methyl-D-aspartate (NMDA) receptor and the σ-subtype 1 receptor, thus having anti-depressive potential. Furthermore, DHEA can play a role in endothelial proliferation and angiogenesis through membrane-bound G-coupled receptor that has been described on vascular endothelial cells [3].

SUPPLEMENTATION OF DHEA AS A HORMONE REPLACEMENT THERAPY IN PREMENOPAUSAL AND POSTMENOPAUSAL WOMEN

Postmenopausal women present sharp drop in estradiol level and rapid rise of FSH. In elderly males slow but continuous, age-dependent decline of testosterone level is observed. The decrease is more pronounced for free testosterone as a result of the age-associated increase of the levels of sex hormone binding globulin (SHBG). Moreover, the circadian rhythm of testosterone secretion is lost in elderly men. The age-associated decrease of DHEA is the most important and ubiquitous decrease of all hormones in all men and women [10]. In contrast to estradiol breakdown, androgens are secreted for many years after menopause. Interestingly some menopausal women, e.g., after bilateral oophorectomy or premature ovarian failure, experience concomitant deficiency of androgens, thus could clearly benefit from DHEA supplementation [11].

Osteoporosis, metabolic health, and muscular strength

DHEA is the precursor for at least 70% of androgens in elderly women, and a major origin of estrogens in males and postmenopausal females. Therefore, it has been suggested that the drop in DHEA level with aging leads to physiological changes that are dependent on steroid hormones, such as the loss of bone density and muscular mass.

A small number of randomized controlled trials have assessed changes in bone mineral density (BMD) in older females on DHEA replacement therapy at doses of 25–100 mg/d. In a randomized controlled trial, the effect of 12-month supplementation with DHEA on BMD in 70 women, aged 60-88 years with low serum DHEAS concentration levels at baseline was investigated [12]. The intervention compared oral DHEA 50 mg/d with placebo for 12 months. Intent-to-treat analyses showed trends towards increase of BMD with DHEA versus placebo at the total hip (1.0%), trochanter (1.2%), shaft (1.2%), and lumbar spine (2.2%). Also, modest effects of DHEA supplementation on bone density in postmenopausal women was observed when treatment time exceed 52 weeks [3].

A recent systematic review with meta-analysis of randomized placebo-controlled studies of DHEA supplementation of BMD in healthy women revealed, that hip and trochanter BMD increased remarkably above control group in individuals, who took DHEA supplementation [13]. During DHEA therapy, serum osteocalcin also increases (from 1.16 to 2.44 µg/L), which is a marker of bone formation [14].

The aging process in women is associated with changes in muscle, that can lead to sarcopenia, and about 20% of patients with sarcopenia are functionally disabled. An important reason for this phenomenon is a marked decline in serum sex steroids – estradiol and DHEA. In postmenopausal women, DHEA becomes the predominant sex hormone, however the relationship among, DHEA, and mass of muscles or strength in women after the menopause has not been documented.

Therefore, the relation between the level of intramuscular steroid hormones and muscle characteristics in menstruating women was investigated [15]. The authors measured isometric skeletal muscle strength, knee extension strength, and explosive lower body muscle power. They concluded that intramuscular estradiol, testosterone, and DHEA are proved significant, independent predictor factors of strength and power that explains 59–64% of the difference in knee extension strength and 80–83% of the difference of vertical jumping height in women. These results suggests that intramuscular sex hormones are related with strength and power level in female muscles.

In most recent study [16] the relationship between sex steroids (DHEA, testosterone and estradiol) muscle mass, and muscle strength in postmenopausal women were investigated. Women classified within the lowest DHEA and free testosterone tertile had lower muscle strength in comparison to those placed in the highest tertile (adjusted OR for DHEA 1.42; 95% CI 1.02–1.99), however, estradiol was not related to muscle strength.

The accumulation of abdominal fat increases with age, and is associated with insulin resistance, diabetes, and atherosclerosis. Hormonal changes (low DHEA levels) that occur with aging may contribute to the increase in abdominal fat. Administration of DHEA to reduce visceral fat accumulation in rats, and has a protective effect against insulin resistance and the decrease in insulin responsiveness. A possible explanation for these findings is that DHEA is an alpha activator of peroxisome proliferator activated receptor α (PPARα), what is associated with favor increasing of fat oxidation and reducing fat deposition.

The influence of DHEA supplementation of insulin metabolism was also investigated in women. In randomized, double-blind, placebo-controlled trial conducted in 28 women with age-related decrease in DHEA level, participants received 50 mg/d for 6 months [17]. DHEA therapy results in significant decreasing in visceral and fat and subcutaneous fat area. Also, the insulin levels decreased, and insulin sensitivity increased during the OGTT after DHEA therapy. So, authors concluded, that DHEA replacement therapy could play a role in prevention and management of the metabolic syndrome associated with abdominal obesity in women. Despite these results, there are no sufficient data in terms of influence of DHEA supplementation on insulin sensitivity as well as lipid profiles in women [3].

Depression, anxiety, cognitive function and mood improvement

Currently, many data indicate, that DHEA modulate many neurobiological actions and there are evidences showing that DHEA concentrations are inversely correlated with ratings of depressed mood [18]. DHEA as well as glucocorticoids take a part in regulation of many physiological mechanisms and play an important role in regulation of affect and its dysregulation. DHEA levels remarkably decrease throughout adulthood but an increase in circulating cortisol level with advanced age has been proved in human. Therefore, it can be interesting to consider the fraction of both hormones in addition to their absolute levels of concentration. Lower DHEA to cortisol ratio may impact many physiological functions, including learning, memory, and is associated with greater cognitive impairment. It has been recently revealed that DHEA treatments improve cognitive deficits and depressive like behaviors in animals by promoting neurogenesis in the hippocampus [19].

In patients with posttraumatic stress disorder (PTSD), which is classified as the anxiety disorder, elevated DHEA concentration was identified, and researchers have suggested, that DHEA may have a role in resilience and in proper adaptation to stressors [20].

Majority of studies have reported lowered serum concentration levels of DHEA in subjects with poor life quality, satisfaction and psychosocial stress. Higher plasma and serum concentrations of DHEAS have also been associated with greater amount, frequency, and enjoyment of leisure activities and psychological profiles associated with health [21].

Clinical trials of DHEA treatment for depression constantly suggest beneficial consequences. Randomized control trials showed that application of DHEA used alone or as an antidepressant adjunct in unresponsive patients with depression, has significant antidepressant effects (as shown by improvements in Hamilton Depression Ratings and Symptom Checklist) in some of them. In most studies, authors stated that baseline serum DHEA concentrations did not predict antidepressant response, responders to DHEA reached higher serum DHEA concentrations following treatment and antidepressant effects were directly correlated with variation in DHEA levels [22, 23]. However, recent data suggest that higher circulating DHEA(S) levels can predict SSRI-associated remission in major depression [24]. It is obvious that, more trials will be necessary to establish the place of DHEA supplementation in therapy of patients with depression, and to compare DHEA to standard antidepressants.

Libido and sexual satisfaction

Sexual desire and libido in women are affected by endocrine factors. Adrenal androgens are necessary for normal sexual function, while disorders characterized by androgen deficiency are associated with a low frequency of sexual activity.

Although testosterone plasma levels do not correlate directly with sexual function in cross-sectional and longitudinal studies, they have the main role in sexual desire [25], On the other hand, it is suggested, that a poor DHEA level negatively correlates with sexual function in women before and after menopause [26].

DHEA supplementation has been recognized for its beneficial effect on sexual function but still the effects of DHEA therapy on sexuality in postmenopausal women are controversial [27], what is mainly associated with dose of DHEA and treatment time.

In most recent study, authors reported the influence of DHEA supplementation in dose of 10 mg daily on sexual function, frequency of sexual intercourse, and quality of relationship early after menopause [28]. Efficacy was evaluated using the McCoy Female Sexuality Questionnaire during 12 months of treatment. DHEA supplementation related to improvement in sexual function, and significant growth in the numbers of sexual intercourses.

The results of DHEA administration on sexual function was also investigated in premenopausal women. This observational study [29] investigated the effect of DHEA in dose 25 mg three times a day on the Female Sexual Function Index (FSFI) in women with mean age 41 years. The FSFI score for the treated group raised by 7%, domain scores for desire raised by 17% and by 12% for arousal, while no difference in domain scores for orgasm or satisfaction were proved. Women starting in the lowest quartile of FSFI score, experienced 34% growth in total FSFI score during treatment with DHEA. Among participants of a trial, improvements in domain categories were shown for desire (40%), arousal (46%), lubrication (33%), orgasm (54%), and sexual satisfaction (24%). This study implies that administration of DHEA improved sexual function in premenopausal women from low baseline FSFI scores group.

Androgen replacement in unselected postmenopausal women has been administrated for decades as an off-label treatment. Recently a global consensus on testosterone replacement for women was formulated [30]. The statement does not support the systemic and local use of DHEA for hypoactive sexual desire disorder (HSDD) in postmenopausal women with proper adrenal function. While, testosterone treatment, in doses that are in normal range of the physiological testosterone concentrations for premenopausal women, results in a beneficial effect on sexual function. Study included increases, above the effects of placebo/comparator therapy, of an average of one satisfying sexual event per month, and increases in the subdomains of sexual desire, arousal, orgasmic function, pleasure, and sexual responsive-

ness. On the other hand, a reduction in sexual concerns including sexual distress was observed.

More adequately powered, double-blind RCTs, with no selection bias and with consistent reporting and analysis of standardized results, are required to comprehensively document the benefits and risks of DHEA and testosterone supplementation in women.

Cosmetic dermatology

DHEA can also be used in cosmetic dermatology. It has been shown to act on the sebaceous glands, increases sebum production in postmenopausal women, and thus prevents the skin from drying out. This effect is due to presence in these cells, the steroidogenesis enzymes necessary for catalyzing the transformation reaction of DHEA to DHT, which is main stimulator of sebaceous gland activity [31]. In addition, DHEA could improve skin hydration reduction of its pigmentation [32].

SUPPLEMENTATION OF DHEA IN WOMEN WITH ADRENAL INSUFFICIENCY AND CHRONICALLY TREATED WITH EXOGENOUS GLUCOCORTICOIDS

Highest beneficial effect of DHEA supplementation was reported in individuals with virtually complete DHEA deficiency that occurs in adrenal insufficiency [11]. Primary or iatrogenic adrenal insufficiency, despite supplementation of glucocorticoids (GKS), leads to decreased quality of life (QoL) when compared to healthy population [33]. DHEA supplementation has been studied as an accessory treatment to conventional adrenal replacement therapy with glucocorticoids and mineralocorticoids. The exact physiological roles of DHEA still remains not fully elucidated and the routine therapy in individuals with adrenal insufficiency is still controversial. Some papers reported significant improvements of mood, well-being, sexual thoughts, libido, interest and satisfaction following DHEA replacement particularly in females [11, 34]. Other analysis of DHEA administration in women with primary and secondary type of adrenal insufficiency have resulted in inconsistent and unreproducible data [35]. According to recent recommendations, supplementation of DHEA is indicated in hypo-adrenal women with low libido, depressive symptoms, low energy levels or impaired sense of well-being despite optimized glucocorticoid and mineralocorticoid replacement [36].

In women with systemic lupus erythematosus, treated with high, that is anti-inflammatory doses of corticoids DHEA reduced disease activity and had an antiosteoporotic effect. One study suggested also benefits for cognitive function in such patients [37].

SUPPLEMENTATION OF DHEA IN WOMEN WITH VULVOVAGINAL ATROPHY

Efficacy and safety of DHEA were also investigated in women with vulvovaginal atrophy due to menopause, also called genitourinary syndrome of menopause (GSM), especially in women suffering from moderate to severe dyspareunia or pain at sexual activity.

In a prospective, double-blind, and placebo-controlled clinical trials with randomization, the effect of intravaginal 0.50% DHEA (6.5 mg per day) was assessed on four coprimary objectives, i.e., percentage of parabasal cells, percentage or superficial cells, level of vaginal pH, and pain at sexual activity (moderate and severe dyspareunia) identified by the women as most troublesome vulvovaginal atrophy symptom. After intravaginal administration of 0.50% DHEA for a period of 12 weeks, the fraction of parabasal cells was decreased by 27.7%, whereas the percentage of superficial cells were increased by 8.44%, vaginal pH was reduced by 0.66 pH, and the pain at sexual intercourse decreased by 1.42 severity score unit from the baseline. On the other hand, moderate or severe vaginal dryness, that was present in 84.0% of women, have improved at 12 weeks by 1.44 severity score unit in comparison to baseline. At gynecological examination vaginal secretions, epithelial integrity, epithelial surface thickness, as well as, color were all improved [38].

The clinical benefits of DHEA therapy demonstrated in 12-week studies, were also confirmed in 52-week study [39]. After 52 weeks of treatment, a significant betterment was seen in comparison to the baseline in parameters such as a decrease in the fraction of parabasal cells, a growth in the fraction of superficial cells, and a decrease in vaginal pH, as well as the volume of vaginal discharge, and vaginal epithelial integrity, thickness and color. In women who suffer from moderate to severe dyspareunia as the most bothersome symptom of GSM, and who met the inclusion criteria of postmenopausal vaginal atrophy, the pain severity score was decreased by 46.7% during 12 weeks period, and further by 19.4% between 12 and 52 weeks, finale reaching the level of 33.9% of the baseline at week 52. In women that suffer from moderate to severe dyspareunia and considered vaginal dryness or vaginal irritation/itching as the most bothersome symptom of atrophy, the pain severity score reduced from 2.42 ± 0.07 at baseline to 0.77 ± 0.12 at week 52. Moreover, in females with moderate and severe vaginal dryness or vaginal irritation/itching, the severity of each of the symptoms after 52 weeks of administrating prasterone decreased also significantly.

SUPPLEMENTATION OF DHEA FOR FERTILITY IMPROVEMENT

Diminished ovarian reserve (DOR) is a common cause of otherwise unexplained infertility, as well as, early ovarian hor-

monal insufficiency and related endocrinopathies. Recently published meta-analysis that included 14 studies shows that individuals with premature ovarian insufficiency (POI) have lower concentration levels of androgens in comparison with healthy controls: DHEAS, testosterone and androstendione [40]. Others estimated that suboptimal DHEAS concentrations are quite common and were found in 65% of women with diminished ovarian reserve DOR [41]. Androgen levels are lower in POI than in women with regular cycles [42]. Autoimmunological disorders can have a role in deregulated function of DHEA on DOR. Occurrence of the anti-thyroid antibodies in women with POI correlated with deeper drop of DHEAS. Treatment with DHEA caused decrease in thyroid peroxidase autoantibodies levels [43]. In a small group consisting of 25 patients with POF high proportion (44% vs. 4%) of autoantibodies was found. Moreover, occurrence of autoimmunity was associated with higher DHEAS level decrease [44].

Supplementation of DHEA in IVF cycles

The DOR is a leading challenge for artificial reproductive technologies (ART), since growing incidence and significant decrease in the effectiveness of stimulation and outcome of *in-vitro* fertilization (IVF). It can be explained by decreased ovarian reserve and reduced oocyte quality. Although, ESHRE recommendations do not support any therapeutic modality in premature ovarian insufficiency promoting oocyte donation in such cases. Moreover, it is indicated that androgen administration has poor evidence in infertility treatment [45]. Up to date, many attempts were done to improve the effectivity of therapy in infertile DOR women. Supplementation with DHEA is one of the solutions to the problem. A recent meta-analysis proved that the rates of clinical pregnancy (CPR) were improved significantly when DHEA pre-treatment was implemented (OR = 1.47, 95% CI: 1.09–1.99). No differences in the number of oocytes retrieved, the cancellation rate, and the miscarriage rate was reported [46]. Other meta-analysis reported supplementation with DHEA as a therapy that improve IVF results in patients with DOR. However, randomized controlled trials did not give a prove for the performance of DHEA therapy, one prospective randomized trial revealed that DHEA may increase potential for fertility in women without DOR [47]. Since females with normal ovarian reserve supplemented with DHEA had a significantly better live birth rate and a lower miscarriage rate [48], it has been even indicated that all women aged above 35 years may be treated with DHEA to diminish the abortion rate and increase treatment effectiveness [49].

The physiological processes underlying advantageous activity of DHEA occurred to be still not fully determined. Supplementation with DHEA rise the number of top-quality embryos, transfers and fertilization rate compared with placebo group. Moreover, supplementation was shown to decrease DNA damage and rate of apoptosis, increase the mitochondrial fraction, and dehydrogenase activity in mitochondria of cumulus oophorus [50]. DHEA administration caused that higher embryo score is associated by changes in follicular fluid constitution that includes variation in bone morphogenic protein-15 (BMP-15) [51]. Other authors reported that DHEA advantageous effect on gonad is caused by reduced concentration of senescence marker: senescence-associated β-galactosidase (SA-β-gal) in cumulus oophorus and in granulosa cells [52]. Administration of DHEA increases the level of androgen receptor (AR) and follicle-stimulating hormone receptor (FSHR) in granulosa cells. Moreover, higher increase was associated with improved results of stimulation [53]. It is known that DHEA, as well as, its downstream metabolites can act by modulation of immune response. The supplementation could also increase the Th1 immune response and change the balance of the Th1/Th2 ratio. Studies on animal model also indicated some mechanisms. DHEA administration may increase T lymphocyte infiltration on murine model, causing a decrease in the CD4+ T lymphocyte population, an increase of the CD8+ T lymphocyte number. Therefore, change in of balance between CD4+/CD8+ T cells take a place [54].

Supplementation of DHEA in natural cycles

Treatment with DHEA has been applied in infertile females with low ovarian reserve who try to conceive spontaneously. One of first case series by Mamas and Mamas described five females with POI supplemented with DHEA. The treatment caused decrease in level of FSH and spontaneous pregnancy in all reported patients that occurred in 1-6 months from start of treatment [55]. DHEA was evidenced to significantly upregulates AMH in patients with DOR. Advantageous outcomes were reported for antral follicle count (AFC), estradiol, inhibin B and FSH concentrations [56–58]. Trials on patients pre-treated with DHEA, because of low ovarian response, reported remarkably high number of spontaneous pregnancies and ongoing pregnancies (21.05% and 13.15% respectively). Recent paper show that 2 in 20 supplemented patients conceived spontaneously in DHEA group [59]. Many small series of cases advocating for implementation of DHEA supplementation in infertile DOR patients that refuses oocyte donation in IVF treatment have been published so far [60].

In the animal model supplementation of DHEA reversed the DOR phenotype and reduced atresia rate of the follicles in rats. After administration animals had increased number of primordial, primary, and growing follicles in comparison to untreated group. However, androgen supplementation did not reverse the phenotype completely and the number

of follicles was still reduced in comparison to control rats without DOR [61].

Studies on rat model of DOR showed that there is a window for DHEA dose. To high dosage of DHEA did not improve the ovarian reserve and pregnancy outcome, but rather induce PCOs-like morphology of gonads and impair fertility. This fact indicates the necessity of personalization of the treatment. Tailoring the dose of DHEA and proper selection of patients that will have improvement thanks to the therapy would increase the effectiveness [62]. Therefore, assessment of DHEA-S level and supplementation of DHEA selectively in low-DHEAS group seems to be reasonable and proper treatment strategy [60].

SIDE EFFECTS OF DHEA SUPPLEMENTATION AND CONTRAINDICATIONS

Common androgenic side effects of DHEA replacement have been reported so far: hirsutism, acne, greasy skin, itching of the skin scalp, abundant vaginal discharge, increased apocrine secretion of sweat and related odor. Some studies reported no such side effects. The side effects were infrequent, mild and well-tolerated. No serious adverse effects have been ever reported [35, 63, 64].

Prior to initiating supplementation with DHEA a complete family and personal medical record should be obtained. Careful gynecological and breast examination should be done periodically. Contraindications and possible benefit-risk profile should be considered before treatment and during follow-up. Temporal and persistent contraindications for DHEA supplementation that should be consider [63] includes:

- hypersensitivity to the substances contained in the formulation,
- non-diagnosed vaginal bleeding, untreated endometrial hyperplasia
- diagnosed breast cancer, history or suspicion of breast cancer
- estrogen-dependent malignancy (diagnosed or suspected)
- pregnancy or breastfeeding
- acute liver disease, elevated liver enzymes, kidney failure
- previously or currently diagnosed venous thromboembolism, known susceptibility to venous thrombosis
- active or recent arterial thromboembolic disease
- prostatic cancer or benign prostatic hyperplasia
- porphyria.

CONCLUSIONS

Currently available clinical trials and meta-analyses indicate that DHEA supplementation **is effective** in the following cases:

- Adrenal insufficiency and chronically treated with exogenous glucocorticoids
- In postmenopausal women with low bone mineral density and/or osteoporosis
- In premenopausal women with sexual disorders and low libido
- Vaginally in women with vulvovaginal atrophy of menopause or genitourinary syndrome of menopause (GSM)

Currently available clinical trials suggest that DHEA supplementation is **probably effective in the some of the following cases**:

- Postmenopausal women with hypoactive sexual disorders
- Infertile women with diminished ovarian reserve (DOR)
- Women suffer from depression and anxiety
- Women with obesity and insulin resistance

Usual daily doses of DHEA that are administrated in clinical trials and regular off-label use are summarized in Table 1. In majority of conditions oral dose of 25 mg of DHEA given two or three times a day is often implemented.

Commonly used dosage range of DHEA supplementation in therapy of diverse medical conditions. Most prevalent dose was bolded. Daily doses above 25 mg are usually split into

Table 1. Usual daily doses of DHEA that are recommended, administrated in clinical trials and regular off-label use

Indication with confirmed effectiveness	Daily dose titration range	Reference
Adrenal insufficiency and chronically treated with exogenous glucocorticoids	25–**50 mg** p.o.	[33–35]
Postmenopausal women with low bone mineral density and/or osteoporosis	25 mg–**50 mg**–100 mg p.o.	[3, 12]
Premenopausal women with sexual disorders and low libido	**75 mg** p.o.	[29]
Vulvovaginal atrophy/genitourinary syndrome of menopause (GSM)	3.25–23.4 mg p. vag. **6.5 mg** p. vag. — on market	[38–39, 63]
Indication with possible effectiveness	**Daily dose titration range**	**Reference**
Postmenopausal women with hypoactive sexual disorders	10 mg–50 mg–90 mg–300 mg–450 mg p.o.	[3, 27–28]
Infertile women with diminished ovarian reserve (DOR)	**75 mg** p.o.	[46–60]
Women with depression and anxiety	30 mg–60 mg–**90 mg**–450 mg p.o.	[22–23]
Women with obesity/insulin resistance	25 mg–**50 mg**–100 mg p.o.	[3]

2–3 parts. Please note that table summarizes example of doses administered in clinical practice that may differ from recommended by manufacturer or are utilized in off-label treatment. Administration and dose of every drug should rely on current medical knowledge and individual clinical assessment

Recent statement of experts of the Polish Menopause and Andropause Society and the Polish Society of Aesthetic and Reconstructive Gynecology provides a comprehensive literature review that supports the use of intravaginal DHEA supplementation. Clinical studies with high level of evidence proves that topical treatment is effective, safe and well tolerated long-term therapy for vulvovaginal atrophy [63].

In a Cochrane Systemic Review [64] regarding the supplementation of DHEA in peri- and postmenopausal women, the authors questioned the effectiveness of DHEA in women, but the overall quality of the studies analyzed in this review was moderate to low. It was unclear if supplementation of DHEA decrease symptoms of menopause since the study outcomes were inconsistent and could not be pooled to obtain an overall effect due to versatile types of measurement. Insufficient results were available to estimate quality of life and menopausal symptoms during DHEA supplementation as well as, there were inadequate reports accessible to compare the effects of DHEA replacement to hormone therapy (HT) for quality of life, menopausal symptoms, and adverse effects.

Conflict of interest

The authors report no conflict of interest.

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