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Review

The therapeutic effect of dehydroepiandrosterone (DHEA) on vulvovaginal atrophy

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ABSTRACT

Vulvovaginal atrophy (VVA) is a chronic disease that mostly occurs in postmenopausal women. After menopause, insufficient sex hormones affect the anatomy of the vagina and cause drastic physiological changes. The main histopathological studies of VVA show that postmenopausal estrogen deficiency can lead to the increase of intermediate/parabasal cells, resulting in the loss of lactobacillus, elasticity and lubricity, vaginal epithelial atrophy, pain, dryness. Although the role of estrogen hormones in the treatment of VVA has always been in the past, it is now widely accepted that it also depends on androgens. Estrogen drugs have many side effects. So, Dehydroepiandrosterone (DHEA) is promising for the treatment of VVA, especially when women with contraindications to estrogen have symptoms. This review is expected to understand the latest developments in VVA and the efficacy of DHEA.

1. Introduction

Perimenopausal and postmenopausal vulvovaginal atrophy (VVA) are primarily associated with symptoms and signs of estrogen loss [1]. About 50% of postmenopausal women suffer from VVA symptoms [2]. Genitourinary syndrome of menopause (GSM) includes vaginal dryness, burning, lack of lubrication, discomfort and pain, urgency, urination and repeated urinary tract infections [3]. Major obstacles to the treatment of VVA include lack of understanding of VVA and insufficient relief of existing symptoms. Experts believe that the term VVA is included in GSM, but more specifically, it applies to the above symptoms and conditions related to genitals, except for urological symptoms [4].

Decreased ovarian estrogen production leads to decreased glycogen content in vaginal epithelial cells, estrogen levels and glycogen, lactobacillus counts and increased vaginal pH [5]. Lack of estrogen stimulation results in pale and dry vaginal labia and reduced the volume of vaginal exudate and other glands. If the estrogen is low, the vaginal epithelium becomes thin, the function of the barrier is lost, vaginal folds are reduced. Otherwise, the lack of estrogen leads to the fusion of collagen fibers and the breakage of elastin fibers, resulting in loss of tissue elasticity [6]. Androgens have a regulatory effect on nerve fiber networks, because testosterone is related to the nerve relaxation of these non-vascular smooth muscles. Administration of testosterone can produce DHEA-derived androgenic effects in ovariectomized animals, because testosterone is related to the nerve relaxation of these non-vascular smooth muscles [7]. Estrogen therapy may be absorbed in the circulation and increase the unhealthy dependence on systemic estrogen. Dehydroepiandrosterone (DHEA)/ dehydroepiandrosterone sulfate (DHEA-S) and its local metabolites are useful for maintaining the normal structure and functional strength of the tissues around the vagina and genitourinary organs [8]. The topical effect of DHEA on the vagina is promising, especially in women with contraindications to estrogen [9].

2. Clinical definition and diagnosis of VVA

In recent years, VVA has been renamed GSM to emphasize the various genital, sexual, and urinary symptoms associated with the anatomical and functional changes in vulva-vaginal tissues caused by menopause [10]. Taking into account the low estrogen status, coupled with the reduction of other sex hormones, leading to the widespread urinary tract and vulva-vaginal symptoms, it is recommended that the International Association for Women's Sexual Health Research and North America change "VVA" to "GSM" [11]. VVA-related symptoms

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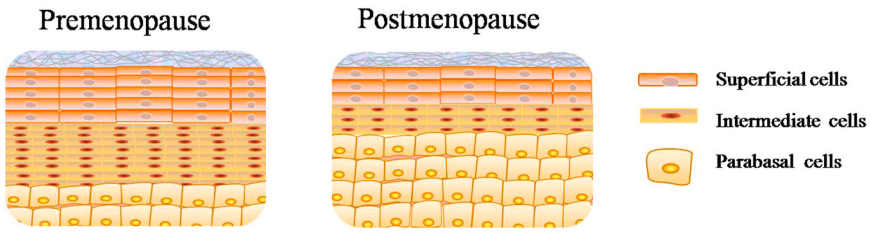

Fig. 1. Comparison of vaginal changes in pre-menopause and post-menopause. Pre-menopausal estrogen helps maintain vaginal folds and replenish the thickness of glycogen superficial cells. The lack of estrogen after post-menopause can lead to an increase in intermediate/parabasal cells, which is manifested as vaginal epithelium atrophy, pain, dryness.

and signs require further research to fully understand the various interferences included in the GSM definition. For clarity in this chapter, we will use the term "VVA" in the following paragraphs.

The most common symptoms of VVA have affected enjoyment of sex (59%), dryness (55%), dyspareunia (44%) and irritation (37%) [12]. The most common diagnosis is based on the patient's description of the condition, sometimes by accurately describing the vulva-vaginal or urinary tract symptoms, but usually it can only be diagnosed by complaining about the decline in quality of sex life, which may lead to misdiagnosis. In addition to clinical symptoms, objective measurements are also used for routine management and endpoints in clinical studies. The FDA's January 2003 vulva and vaginal guidelines to assess VVA have three main common endpoints: 1) Cytology (maturation index-parabasal and superficial cells); 2) vaginal pH; 3) Severity of the most troublesome symptoms(MBS) [13]. The MBS score is a useful tool for measuring subjective symptoms and identifying risk factors for VVA/GSM [14]. The vulvar health index is based on the severity of the vulva and the severity of the symptoms of vaginal atrophy. In this case, a higher score means that the scale of the vulva shrinks [15]. The most commonly used is to assess vaginal pH and The vaginal maturity index (VMI) [16]. The VMI confirms the presence of vaginal atrophy, indicating that compared with superficial cells, the percentage of parabasal and intermediate cells has increased [17]. When parabasal cells are predominant, it is indicative of hypoestrogenemia and atrophy, so transfer to more superficial cells is the primary endpoint of any treatment to relieve symptoms of VVA [18]. The atrophic vaginal epithelium lacks estrogen, has less glycogen content, and presents a higher vaginal pH, which is conducive to the growth of pathogens [19]. Using a technique for measuring vaginal pressure, the general and position of the contact pressure can be measured to determine whether there is pressure expansion. Vaginal electric waves (electric vaginal chart) can measure vaginal muscle contractions [20]. Vaginal photography is a test that measures female sexual arousal and is usually used to assess female sexual dysfunction.

3. Pathology of VVA

3.1. Role of estrogen deficiency in VVA

The vagina is a major factor in women's health perception and quality of life. The common root cause of estrogen deficiency is natural menopause, but breastfeeding and premature ovarian failure (POF) may also cause this condition [21]. The level of estrogen in the circulation is reflected in the physiological and symptomatic changes of the vagina, which leads to a decrease in the epithelial barrier and lubrication function, vaginal glycogen content, the presence of lactobacilli and atrophic vaginitis [22]. It acts on the vagina, vulva, urethra and bladder triangle through estrogen receptors. Serum estrogen levels in normal premenopausal women range from 40 to 400 pg/ml, and fall below 20 pg/ml during the postmenopausal pause [23]. Vaginal health is defined as the state of the vagina that maintains sufficient physiological conditions as women age, which does not produce local symptoms and allows for a satisfactory sex life [24]. It is necessary to maintain the integrity of the tissue and not to disrupt the normal function of vaginal microbe. Therefore, estrogen levels play an important role. VVA is mainly caused by estrogen deficiency. It acts on the vagina, vulva, urethra and bladder triangle through estrogen receptors [25]. Pre-menopausal estrogen helps to maintain the collagen content, thickness and elasticity of the epithelium; it helps to maintain acid mucopolysaccharide and hyaluronic acid to keep the epithelial surface moist [26]. Postmenopausal estrogen deficiency can lead to an increase in intermediate/para-basal cells, resulting in loss of lactobacilli and elasticity and lubricity, manifested by vaginal epithelial atrophy, pain and dryness, reduced vaginal blood flow and increase vaginal pH. The vagina, vulva, pelvic floor muscles, pelvic fascia, urethra and bladder triangle show numerous estrogen receptors (ER, α and β), which can be restored and localized by using systemic hormones Estrogen therapy [27]. ER is mainly expressed in the epithelium, stroma and muscle cells of the human vagina. Estradiol controls many cellular pathways that regulate growth and proliferation, barrier function, and pathogen defense. The main result of lack of estrogen stimulation is the loss of tissue elasticity by inducing the fusion and transparency of collagen fibers and the breakage of elastic fibers. The mucous membranes of the vagina and Labia minor become thinner, paler and less hydrated [28]. As vaginal wrinkles (epithelial folds that allow expansion) gradually disappear, the vaginal canal becomes shorter and narrower. In addition, vascular support is significantly reduced, resulting in a decrease in a lot of vaginal exudates and other glandular secretions [29]. Matrix metalloproteinases (MMT2 and 9) and cathepsins can cause collagen degradation in postmenopausal women [30]. Cell acidic adhesion and hyaluronic acid in the dermis decrease significantly with age. Moreover, para-basal cells gradually dominate, with fewer middle and surface cells (Fig. 1). This means that the vaginal squamous epithelium is completely deprived of estrogen. As a result, it becomes fragile after being susceptible to trauma, ecchymosis, ulcers, and bleeding [31].

3.2. Androgen and vaginal function

The four main androgens in the systemic circulation of premenopausal women are DHEA, androstenedione, testosterone, and 5a-dihydrotestosterone (5a-DHT). The synthesis of androgen mainly occurs in the ovaries and adrenal glands, but it can be synthesized in peripheral tissues [32]. The lack of androgen in the vaginal tissue can lead to VVA and urogenital syndrome during menopause, resulting in decreased lubrication and difficulty in sexual intercourse [33]. Androgen has a regulatory effect on the nerve fiber network because testosterone is related to the nerve relaxation of these non-vascular smooth muscles. Even androgen receptors (AR) are also expressed at various levels (mucosa, submucosa, interstitium, smooth muscle and vascular endothelial), affecting neurovascular and neuromuscular functions under different endocrine conditions [34]. ARs are transcription regulators activated by ligands. The binding of testosterone or 5a-DHT to AR in target cells leads to the dissociation of Heat shock protein (HSP), conformational changes of AR and receptor dimerization [35]. The ligand-bound receptor dimer binds to AREs (androgen-response elements, AREs) on the DNA (Figure2). Such specific binding of

androgen-response elements recruits transcription factors and co-activators or co-inhibitors, resulting in an increase or decrease in androgen, mRNA expression of hormone-responsive genes and subsequent changes in protein synthesis and cell metabolism [36]. The administration of testosterone induces protein gene products in ovariectomized animals. It increases the protein gene product 9.5 (PGP 9.5), which makes these fibers thicker and produces DHEA-derived androgenic effects [37]. Androgen is very important for the differentiation of the vagina. Testosterone is responsible for the structural integrity of vaginal tissues (including the thickness and contractility of vascular smooth muscle and the firmness of collagen fibers) and the relaxation of vascular smooth muscle through the NO/cGMP/PDE5 pathway, nerve fiber density and neurotransmission regulating arousal, and lubrication complex neurovascular [38]. Testosterone regulates nociception, inflammation and mucin secretion in the vagina. In the ovaries, adrenal glands and peripheral tissues, DHEA and androgen can be converted into testosterone, and testosterone can be converted into a stronger androgen 5a-DHT by the action of 5a-reductase, and it can also be converted into estradiol by aromatase. Aromatase also converts androstenedione into estrogen, which is a weaker estrogen. The reversible reaction mediated by multiple isomers of 17b-hydroxysteroid dehydrogenase can mutually convert estrone and estradiol, but estrogen (18-carbon steroid compound) generally does not convert back to androgen [39]. In postmenopausal women, circulating DHEA and androstenedione are important precursors for the local synthesis of testosterone and estradiol in extra-gonadal tissues.

4. Current treatment options and their limitations

4.1. DHEA is promising in VVA women with contraindications to estrogen

DHEA is the most abundant circulating steroid pre-hormone in humans and the main precursor of natural estrogen [40]. In humans, 99% of DHEA is reversibly catalyzed by the sulfotransferase (SULT2A1) to circulate in its sulfated DHEA-S form [41]. DHEA is mainly produced by the adrenal cortex and is rapidly sulfates into DHEA-S [42]. In women, the main sites for androgen production are the adrenal cortex and ovary, mainly DHEA and its sulfates conjugated sulfate DHEAS [43].

DHEA and selective estrogen receptor modulators (SERMS) are currently recommended by IMS (International Menopause Society) or the treatment of VVA/GSM. The use of DHEA for the treatment of VVA is promising, especially in the case of related symptoms in women with contraindications to estrogen [44]. As we all know, estrogen has a great stimulating effect on the proliferation of the endometrium and increases the risk of endometrial cancer. When supplemented with DHEA, it can stimulate the vagina but not the endometrium [45]. It counteracts the over-stimulation of the endometrium caused by estrogen and prevents endometrial cancer. After menopause, DHEA is mainly derived from the exclusive source of inactive precursor transforming steroids from the adrenal glands and becomes the only source of estrogen and androgen in all cells [46]. Recent studies have shown that local delivery of DHEA into the vagina can effectively treat dyspareunia and dryness caused by VVA, but it can also restore the sexual sensitivity of the genitals, so it is easier to obtain orgasms [47]. DHEA replacement therapy is an effective treatment method that minimizes the risk of estrogen treatment, while providing estrogen and androgen for normal vaginal function Fig. 2.

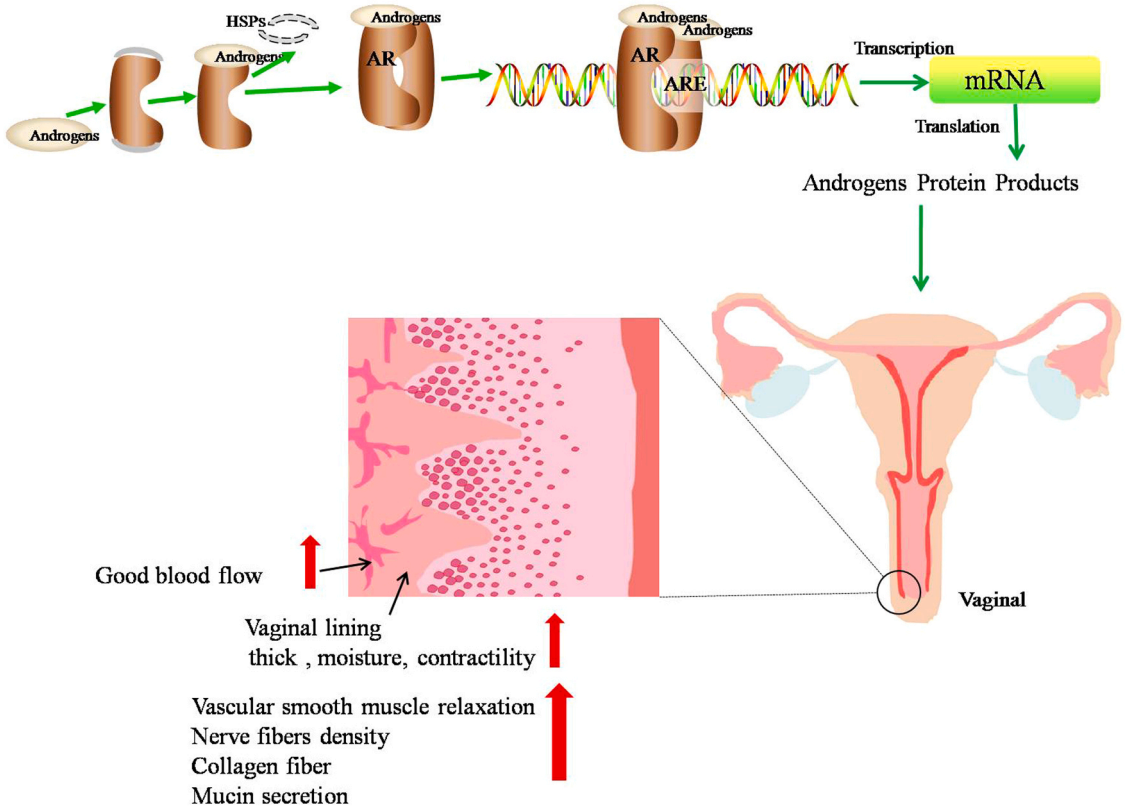

Fig. 2. Androgens participate in vaginal nutrition through AR signals. The binding of testosterone and AR will cause the conformational change of AR, dimerization of the receptor and the dissociation of HSP. At this time, the receptor dimer binds to the ARE on the DNA and organizes to produce a variety of transcription factors, which produce nutritional effects on vaginal tissues through androgen-dependent protein products. Androgen makes the thickness and contractility of vascular smooth muscle and the firmness of collagen fibers, relax vascular smooth muscle, regulate nerve fiber density and neurotransmission, and lubricate complex nerves and blood vessels. Androgen regulates vaginal nociception, inflammation and mucin secretion. *Abbreviations:* HSPs: Heat shock proteins; AR: androgen receptors; ARE: androgen-response element; mRNA: messenger RNA.

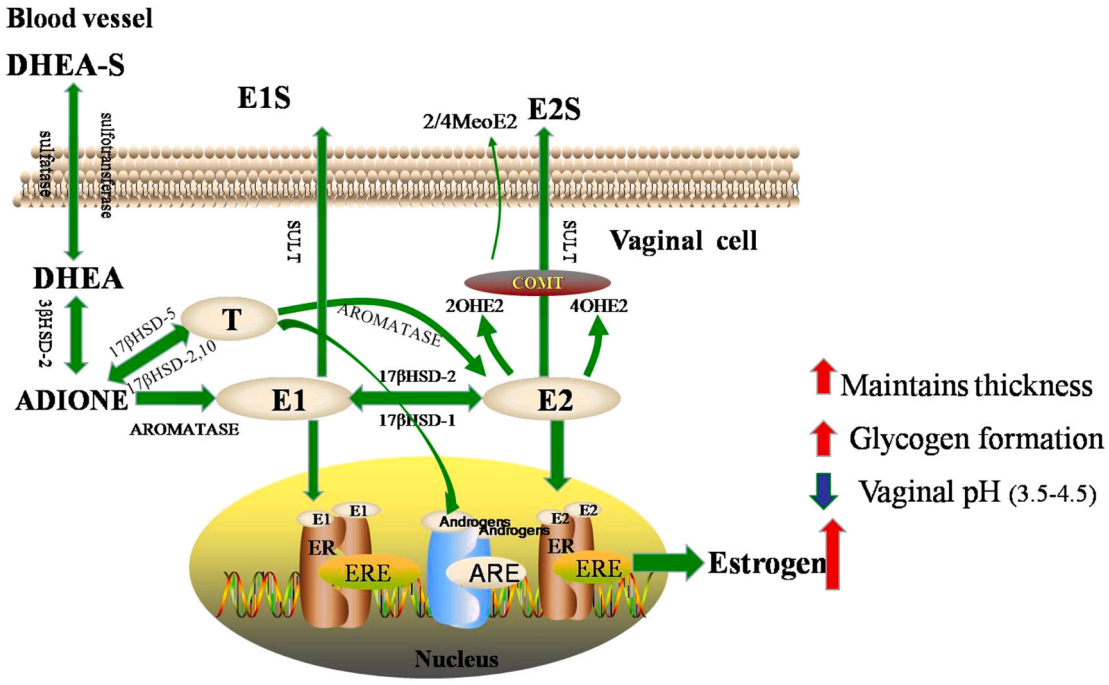

Fig. 3. Mechanisms of DHEA in treating VVA. DHEA is converted by vaginal mucosal cells into estrogen, including estradiol, and into androgens, including testosterone. In surrounding tissues, DHEAS is desulfurized and estrone can be formed through the activities of 3-β-steroid dehydrogenase (HSD), 17-β-HSD and aromatase. Estrone can be combined with estrone sulfate (E1S) to form estrone reservoirs in the blood and tissues; And Estrone can be transformed through 17-β-HSD, which eventually leads to the local formation of free E2. The main pathway of estrogen metabolism is the formation of CYP1A1 and CYP1B1 catalyzed catechol estrogens (CEs) 2- and 4-hydroxyestrogens through hydroxylation, respectively. CEs may be further converted into more stable methoxy derivatives by catechol-O-methyltransferase (COMT). *Abbreviations:* DHEA: Dehydroepiandrosterone; DHEA-S: DHEA–sulfate; E1: estrone; E1S: estrone sulfate; A-dione: 5-androstene-3β, 17β-diol; E2: estradiol; ER: estrogen-receptor; ERE: estrogen-receptor element; E2S: estradiol sulfate; COMT: catechol-O-methyltransferase; CYP19A1: aromatase; 3β-HSD: 3β-hydroxysteroid dehydrogenase; AR: androgen receptors; ARE: androgen-response element.

4.2. How does DHEA really work?

The total amount of DHEA secreted by the ovaries after menopause is about 20% of the total DHEA, because there is no regulatory mechanism that stimulates DHEA secretion when serum DHEA is low, the only way to correct DHEA deficiency is to provide exogenous DHEA to compensate for postmenopausal DHEA deficiency [48].

DHEA and DHEA-S provide about 75% of estrogen for premenopausal women [49]. Circulating DHEA can be locally converted into androgen and estrogen in the genitourinary system tissues, thereby combining AR and ER. Traditionally, it is believed that the effect of DHEA is mediated by its conversion into testosterone and estradiol, and testosterone and estradiol activate the receptors of androgen and estrogen, thereby causing their respective hormonal effects [50]. DHEA also involves a variety of other receptors as well as its oxygenated metabolites, including peroxisome proliferator activated receptor alpha (PPARα), pregnane X receptor [51].

DHEA is metabolized to other steroid hormones, testosterone, DHT or E2 and these metabolites bind to the corresponding steroid receptors: DHEA metabolite 5-androsten-3β, 17β-diol can bind to estrogen with ER-β, which has an effect on sex steroid levels. In surrounding tissues, DHEA-S is desulfurized, and estrone can be formed by the activities of 3-β-steroid dehydrogenase (HSD), 17-β-HSD and aromatase. During vaginal secretion, the inactive sex steroid precursor DHEA penetrates the vaginal cells and is converted into estrogen and androgen in the cell according to the cell type, thereby producing rapid benefits for VVA [52]. Estrone can be combined with estrone sulfate (E1S) to form estrone reservoirs in the blood and tissues. Estrone can be transformed by 17-β-HSD, which eventually leads to the local formation of free E2. The main pathway of estrogen metabolism is to form CYP1A1 and CYP1B1 catalyzed catechol estrogens (CEs) 2- and 4-hydroxyestrogens through hydroxylation [53]. CEs may be further converted into more stable methoxy derivatives by catechol-O-methyltransferase (COMT) (Fig. 3).

4.3. The clinical application of DHEA

DHEA replacement therapy can minimize the risks associated with potential estrogen therapy and it acts precisely on the vagina and provides the required estrogen and androgen. Compared with the different doses of 6.5 mg, 13 mg, and 23.5 mg of DHEA, it was found that the vaginal pH of the highest dose of premenopausal women decreased, the vaginal cell maturation index improved and the level of DHEA was normal. The clinical experience has shown that estradiol (released 7.5 μg per day) or compound estriol (0.5 mg vaginally twice a week) is more effective than 10 μg estradiol vaginal tablets twice a week [54]. The Labrie study found that compared with the placebo group, the DHEA treatment group received 0.50% DHEA (6.5 mg) daily dose of vaginal treatment for 12 weeks, the percentage of para-basal cells decreased and the surface cells increased. The vaginal pH decreases, vaginal dryness and pain during sexual activity are improved [55]. At the same time, according to the Female Sexual Function Index (FSFI) questionnaire, it was found that all aspects of sexual desire, arousal, lubrication, orgasm, satisfaction and pain were improved [56]. DHEA plays an important role in resolving the symptoms of vaginal atrophy, while improving energy levels and mental alertness and providing cardiovascular protection by lowering cholesterol. This review provides the clinical citation data of DHEA in the treatment of VVA (Table 1).

5. Conclusion and future perspective

In this comprehensive review, different opinions summarize the possibility that DHEA can treat VVA. This article briefly introduces the latest research on potential applications. VVA is defined as a variety of genitourinary complications. Although a lot of research work has been

Table 1
Summary of clinical studies on DHEA for VVA treatment.

Source	Duration	DHEA administered	Evaluation index	Outcome
Labrie et al. [60]	7 Days	6.5 mg (n = 10) 13 mg (n = 10) 23.4 mg (n = 10) Placebo (n = 10)	Serum steroid levels of DHEA, DHEA-S,Androst-5-ene-3,5-diol, DHT,Testosterone,4-dione,E2,E1 ,E1-S,ADT-G,androstane-3,3-diol-3G,3-diol17G	The clinically effective dose of 6.5 mg of DHEA administered intravaginally will not be significantly released in the circulation E2 or testosterone.
Labrie et al. [61]	12 W	3.25 mg (n = 53) 6.5 mg (n = 56) 13 mg (n = 54) Placebo (n = 53)	Sexual desire, intimacy avoidance and vaginal dryness	The dose of 6.5 mg of DHEA can improve sexual desire, arousal, arousal/lubrication and summary scores of the ASF questionnaire, vaginal dryness, and all sexual areas of the MENQOL questionnaire
Ke et al. [62]	52 W	6.5 mg DHEA	The serum levels of DHEA, DHEA-S,androstene-3β,5-diol,4-dione,testosterone,DHT,E1,E2,E1-S, ADT-G,androstane-3α,3α-diol-17G	All serum steroids were kept within normal values, and there was no significant difference between treatment times.
Labrie et al. [63]	12 W	0.50%DHEA (n = 66) Placebo (n = 34)	Vaginal dryness, severity score	Among the partners receiving DHEA treatment, 90% of men did not feel their partner's vaginal dryness
Portman et al. [64]	52 W	3.25 mg (n = 126) 6.5 mg (n = 129) 13 mg (n = 30) Placebo (n = 133)	Endometrial biopsy	Even after systemic administration in high doses, DHEA has proven to have no stimulating effect on the human endometrium.
Ke et al. [65]	12 W	0.50%DHEA (n = 325) Placebo (n = 157)	The serum levels of DHEA, DHEA-S,Androst-5-ene-diol-3,5-diol,testosterone,DHT,4-dione,E1,E2,E1-S, ADT-G,androstane-3α,3α-diol-17G	DHEA causes local effects in the vagina without systemic exposure to sex steroids.
Labrie et al. [66]	12 W	0.50%DHEA (n = 325) Placebo (n = 157)	The six domains and total score of the FSFI questionnaire	The benefits of intravaginal DHEA for female sexual dysfunction, sexual arousal and lubrication, orgasm, increased sexual satisfaction, and decreased pain during sexual activity.
Bouchard et al. [67]	12 W	0.25% DHEA (n = 128) 0.50% DHEA (n = 125) Placebo (n = 130)	Vaginal cell maturation,Vaginal pH, Vaginal dryness	Daily intravaginal administration of 0.50%DHEA for 12 weeks has shown clinical and statistically significant effects on moderate to severe dyspareunia.
Bouchard et al. [67]	12 W	0.25% DHEA (n = 85) 0.50% DHEA (n = 85) Placebo (n = 85)	Vaginal parabasal cells, vaginal superficial cells, vaginal pH, dyspareunia	The treatment group showed a decrease in the percentage of parabasal cells and an increase in the percentage of superficial cells. The epithelial surface has improved thickness and color. Serum steroids remained within the normal range of postmenopausal physiology.
Labrie et al. [68]	52 W	Daily intravaginal administration of 0.5% DHEA	Vaginal cell maturation Vaginal pH	MS symptoms with or without MBS will not affect the observed duration or magnitude of DHEA treatment.
Labrie et al. [69]	12 W	0.50% DHEA (n = 325) Placebo (n = 157)	Parabasal cells, superficial cells, vaginal pH, sexual activity	Daily intravaginal plasma 0.50% DHEA results show that it can reduce the percentage of parabasal cells and vaginal pH, increase the percentage of superficial cells, reduce pain related to sexual activity, improve moderate to severe vaginal dryness, and maintain serum steroid levels after menopause.
Bouchard et al. [70]	52 W	Daily intravaginal 0.50% DHEA (n = 145)	The FSFI questionnaire (desire, arousal, lubrication, orgasm, satisfaction, pain)	The DHEA treatment group increased FSFI domain desire, arousal, lubrication, orgasm, satisfaction.
Montesino et al. [71]	12 W	0.50% DHEA (n = 254) Placebo (n = 119)	The acceptability of the procedure of administration of intravaginal DHEA with an applicator	Intravaginal injection of DHEA ovules/suppositories on the acceptance of VVA in women indicated that approximately 92–94% of women said that they would be successful in using applicators and applicators in the future.
Labrie et al. [72]	12 W	0.50% DHEA (n = 436) Placebo (n = 260)	Pain at sexual activity, parabasal cells, superficial cells, vaginal pH	The percentage of parabasal cells decreased, the number of epidermal cells decreased, the vaginal pH value decreased on average, the severity score of most troublesome symptomatic dysmenorrhea decreased and the severity score of MS vaginal dryness decreased.

Abbreviations: ASF: Abbreviated Sexual Function; MENQOL: Menopausal Specific Quality Of Life; DHEA-S: DHEA-sulfate; 5-diol: 17β-diol; 4-dione:androstenedione; DHT: dihydrotestosterone; E1:estrone; E2:estradiol; E1-S:E1-sulfate;ADT-G: androsterone glucuronide; 3α-diol-17G: androstane-3α, 17β-diol 17-glucuronide; FSFI: Female sexual function index; VVA: vulvar atrophy; MBS: the most bothersome symptom; MS: moderate/severe symptoms.

conducted in the past two decades, there is still a big gap between academic research and clinical trials. The gap may be due to the lack of sufficiently effective in vitro and in vivo animal models to simulate the pathophysiological conditions involved in the overall pathogens of VVA. In addition, because the onset of clinical symptoms of VVA is long (possibly as long as decades), it has research value for preventing or delaying the onset of VVA. Finally, the identification of VVA-related biomarkers may supplement the therapeutic significance of VVA.

For the current treatment of VVA/GSM, the biggest obstacle to vaginal estrogen therapy is the fear of potential side effects, including the increased risk of endometrial and breast cancer, stroke, deep vein thrombosis, pulmonary embolism, and myocardial infarction (Table 2). Although DHEA targeted treatment, there is a lack of research on absorbed or metabolite blood level changes and how the drug is passed vaginal absorption. Due to the mechanism of the disease, the administration of estrogen can increase vaginal blood flow, and improve vaginal elasticity and lubrication. It remains the gold standard for the treatment of the disease and can be used systemically and locally [57]. However, high levels of estrogen can have a negative effect and may increase the risk of breast cancer, endometrial cancer and uterine cancer, which may lead to the fact that most women would rather suffer pain than seek treatment [58]. Androgen is also common clinical drugs for the treatment of this disease. When exogenous testosterone is absorbed into the blood, androgen produced in vaginal target cells promote the production of lower vaginal epithelial cells and improve the maturity index of vaginal cells. Androgen can be partially transferred to estrogen to play a role. However, long-term use of androgens can also cause some adverse effects, such as abnormal liver function, hyperlipidemia, weight gain, hair and virilization [59]. Current data have confirmed that the local administration of DHEA can rapidly obtain

Table 2
Comparison of DHEA and estrogen in VVA treatment.

	Low dose vaginal estrogen	Vaginal DHEA
Prescription [73]	Prescription only	Prescription only
Dryness and irritation	Yes [73]	More stronger [55,73]
Vaginal musculature	Improvements in vaginal musculature	Improvements in vaginal musculature
Pain during intercourse	Reduced [9]	Reduced [9]
Libido, sexual satisfaction	Possibly [74]	Yes [74]
Bone formation	Not found [75]	Yes [75]
Hot flushes	Possibly [76]	Reduced [77]
Endometrial hyperplasia or cancer	Yes [64]	No [64]
Side effect	Venous thromboembolism, stroke and hormone-dependent cancer [12], Severe breast pain [75] Estrogenic cancer tumors [78]	Doses of 50 mg and above have shown androgenic side effects (acne and hirsutism, hair loss) [79,80] Atypical cells of undetermined significance (ASCUS) , Low-grade squamous intraepithelial lesions (LSIL) [68]

beneficial effects on vaginal atrophy through its intracellular transformation, without systemic exposure to sex steroids, thereby avoiding the increased risk of breast cancer.

DHEA has shown great potential in the treatment of postmenopausal diseases. Women using topical, minimally absorbed topical treatments will not increase the risk of these diseases, but this still needs to be verified.

Author contributions

Wang J. contributed to paper writing and performed the analysis with constructive discussions. Wang L. contributed the conception of the study, review design and paper writing.

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Conflict of interest statement

The authors declared no conflict of interest.

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