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REVIEW ARTICLE

The vagina as source and target of androgens: implications for treatment of GSM/VVA, including DHEA

S. Cipriani[a,b], E. Maseroli[a], S. A. Ravelli[b] and L. Vignozzi[a,b,c]

[a]Andrology, Women's Endocrinology and Gender Incongruence Unit, Careggi University Hospital, Florence, Italy; [b]Department of Experimental and Clinical Biomedical Sciences 'Mario Serio', University of Florence, Florence, Italy; [c]Istituto Nazionale Biostrutture e Biosistemi (INBB), Rome, Italy

ABSTRACT

The vagina is traditionally thought of as a passive organ in the female reproductive system, serving primarily as a passageway for menstrual blood, sexual intercourse and childbirth. However, recent research has shed light on the vagina's role as an endocrine organ that plays a crucial role in female hormonal balance and overall health. Particularly, growing evidence shows that the human vagina can be considered both as source and target of androgens, in view of the novel concept of 'intracrinology'. Besides the well-known role of estrogens, androgens are also crucial for the development and maintenance of healthy genitourinary tissues in women. As androgen levels decline with age, and estrogen levels fall during the menopausal transition, the tissues in the vagina, together with those in the urinary tract, become thinner, drier and less elastic, leading to a variety of uncomfortable and sometimes painful symptoms, clustered in the genitourinary syndrome of menopause (GSM). Given the lack of testosterone-based or androstenedione-based products approved by regulatory agencies to treat GSM, the possibility of using intravaginal prasterone, which works by providing a local source of dehydroepiandrosterone (DHEA) to the vaginal tissues, appears to be a targeted treatment. Further studies are needed to better assess its safety and efficacy.

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Introduction

The vagina is traditionally thought of as a passive organ in the female reproductive system, serving primarily as a passageway for menstrual blood, sexual intercourse and childbirth. However, recent research has shed light on the vagina's role as an endocrine organ that plays a crucial role in female hormonal balance and overall health [1].

Throughout a woman's life, the vagina shows a significant plasticity, and is sensitive to a variety of hormones and growth factors, including estrogen, progesterone and androgens. These hormones play important roles in regulating the vaginal environment, including pH levels, moisture and bacterial balance, and also the neurovascular mechanisms that underlie the female sexual response [2].

Specifically, androgens have been typically associated with male development and reproductive function; however, in women they can be found in greater amounts than estrogens most of the time [3], and they are crucial for the development and maintenance of healthy vaginal tissues. Indeed, androgens stimulate the growth and functioning of the clitoris, labia and other external genitalia, as well as those of the internal vaginal tissues [1]. The most active androgens, namely testosterone and dihydrotestosterone (DHT), are produced locally within the vagina through the action of enzymes such as 5α-reductase, starting from the circulating precursor dehydroepiandrosterone (DHEA).

As androgen levels decline with age, beginning in the early reproductive years [4], and estrogen levels fall during the menopausal transition, the tissues in the vagina, together with those in the external genitalia, urethra and bladder, become thinner, drier and less elastic [5]. This can lead to a variety of uncomfortable and sometimes painful symptoms, such as vaginal dryness, itching, burning, pain during sex and urinary incontinence or urgency [6]. These symptoms, clustered in the genitourinary syndrome of menopause (GSM), can significantly impact a woman's quality of life, but many patients are hesitant to seek treatment due to embarrassment or lack of awareness about available options.

While local estrogen therapy is overall effective in treating GSM-related vulvovaginal atrophy (VVA) [7], this approach overlooks an essential target in the restoration and promotion of vaginal health: the androgen signaling pathway.

In this review, we present emerging data and recently confirmed evidence that convincingly support the role of the vagina as an endocrine organ, acting as a source and target of androgens, and the clinical implications for the treatment

CONTACT Linda Vignozzi linda.vignozzi@unifi.it Department of Experimental, Clinical and Biomedical Sciences 'Mario Serio', University of Florence, Viale Gaetano Pieraccini 6, 50139 Florence, Italy.

of GSM/VVA, including the recently approved intravaginal DHEA.

Methods

An extensive literature search (2002–2023) for peer-reviewed publications on the role of androgens in women, including their vaginal source and effects, as well as their possible employment for the treatment of GSM, was performed using the PubMed database. We based the current narrative review on this search. We principally selected articles in English, excluding dissertations, correspondence, duplicates and irrelevant literature.

The role of androgens in women

Although estrogens are considered the dominant sex steroid in the female gender, in fact, quantitatively, women secrete greater amounts of androgens than of estrogens. The exception is represented by the pre-ovulatory and mid-luteal phases of the cycle, when their levels are similar [8]. Therefore, it is not surprising that androgens exert fundamental physiologic effects in women.

The major circulating androgens, in descending order of concentration, are DHEA sulfate (DHEAS), DHEA, androstenedione, testosterone and DHT, although only the latter two bind the androgen receptor (AR) (Table 1). Androgens are primarily produced by the ovaries, in the theca cells of developing ovarian follicles, and by the adrenal glands, in the zona reticularis of the cortex. Their synthesis is stimulated mainly by luteinizing hormone (LH) in the ovaries, and by adrenocorticotropic hormone (ACTH) in the adrenals. Depending on the tissues, they can be converted into different metabolites (Figure 1).

Relating androgens to physiological or pathological processes is challenging, primarily due to our lack of knowledge of steroid metabolism and inefficiencies in accurately measuring testosterone levels with the commonly used methods [11]. Nevertheless, androgens have been implicated in several major aspects of women's health: the development of sex organs and secondary sexual characteristics, such as pubic and underarm hair, and breast development; reproductive function, since they contribute to regulate folliculogenesis; sexuality and sexual function, including desire, arousal, lubrication and orgasm; mood, energy levels and sense of well-being; and bone density and composition [11]. Among these areas, the strongest evidence stems from preclinical and clinical research on sexual function.

Specifically, meta-analytic data have shown that women with higher endogenous levels of total testosterone, free testosterone and free androgen index may have a higher sexual desire and overall better sexual function than those with lower levels [12]. Additionally, based on randomized clinical trials (RCTs), a recent global consensus concluded that systemic administration of testosterone to postmenopausal women complaining of low libido, aimed at maintaining physiological premenopausal levels, is a safe and effective strategy [13].

Regarding the genital tissues, supplementation of androgens in ovariectomized animals induces tissue-specific responses, such as changes in AR and estrogen receptor (ER) expression, cell growth, increased perfusion, neurotransmitter synthesis, mucin production and collagen turnover [9]. Within the vaginal layers, testosterone appears essential for the integrity of vaginal tissue structure (including non-vascular smooth muscle thickness and contractility), and for the complex neurovascular processes that are necessary for arousal and lubrication: vascular smooth muscle relaxation via the nitric oxide (NO)/cyclic guanosine monophosphate/phosphodiesterase 5 signaling pathway [14], nerve fiber density and neurotransmission [1]. In addition, activation of the AR in vagina smooth muscle cells has been reported to negatively modulate the immune response and acute and chronic inflammation processes, thus making androgens ideal candidates for the management of GSM, in which inflammation acts as a subtle underlying factor [15].

The vagina as source and target of androgens: vaginal intracrinology

Interesting data about the beneficial effects of androgens on female genital tissues derive from studies conducted on animal models and concern various aspects, including blood flow regulation, the mechanisms of muscle relaxation/contractility and the modulation of inflammatory processes at this level.

Table 1. Characteristics of androgens in women.

Androgen	*Production rate*	*Circulating levels*	*Origin*	*Relative potency*
DHEAS	3.5–20 mg daily	75–375 µg/dl (2–10 µmol/l)	100% adrenals	0.001
DHEA	6–8 mg daily	0.2–0.9 µg/dl (7–31 nmol/l)	50% adrenals 20% ovaries 30% peripheral conversion of DHEA	0.01
Androstenedione	1.4–6.2 mg daily	160–200 ng/dl (5.6–7 nmol/l)	50% adrenals 50 % ovaries	0.1
Testosterone	0.1–0.4 mg daily	20–60 ng/dl (0.70–2.08 nmol/l)	25% adrenals 25% ovaries 50% peripheral conversion of androstenedione	1
DHT	Variable	0.1 nmol/l	100% peripheral conversion of testosterone	5

Adapted from Cipriani et al. [9]. DHEA, dehydroepiandrosterone; DHEAS, dehydroepiandrosterone sulfate; DHT, dihydrotestosterone.

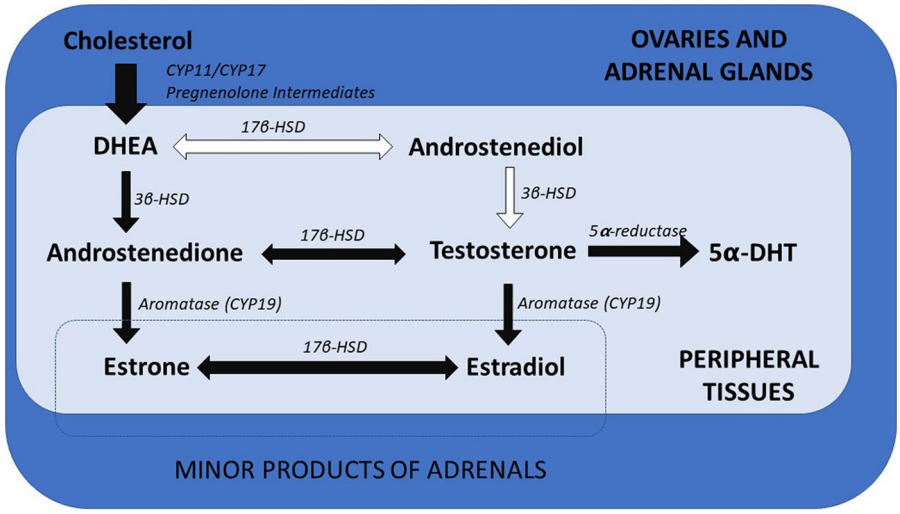

Figure 1. Synthesis of androgens in women. Dehydroepiandrosterone (DHEA) represents the major androgen secreted by the adrenals, starting from cholesterol, by cytochrome P450 11 (CYP11) and CYP17. Testosterone is synthesized from cholesterol in the ovaries and adrenals, and from circulating DHEA in the peripheral tissues. Testosterone and androstenedione are aromatized by CYP19 into estradiol and estrone, respectively. Estrogens are considered a minor product of the adrenal glands. Interconversion between estradiol and estrone is mediated by isoforms of 17β-hydroxysteroid dehydrogenase (17β-HSD). In target tissue, 5α-dihydrotestosterone (5α-DHT) is synthesized from testosterone by 5α-reductase. Major pathways of synthesis are denoted by black arrows and minor by white arrows. Adapted from Traish et al. [10].

In an ovariectomized Sprague Dawley rat model treated with vehicle or different doses of testosterone, and compared with intact rats, Traish et al. evaluated vaginal blood flow in response to pelvic nerve stimulation by laser Doppler flowmetry [16]. The blood flow was significantly reduced in ovariectomized rats and normalized in those treated with testosterone. Ovariectomy also increased the expression of ERs and reduced that of ARs in the vagina, while testosterone therapy increased the expression of both receptors. Infusion of testosterone, even at supraphysiological concentrations, did not change plasma estradiol levels compared to ovariectomized rats treated with vehicle alone, and the vaginal epithelium of testosterone-infused rats remained atrophic, indicating that testosterone was not significantly aromatized to estrogens in the vagina [16]. The authors concluded that testosterone regulates the expression of ARs and ERs in the vagina and improves vaginal perfusion with an androgen-dependent mechanism, playing an important role in modulating vaginal physiology and contributing to the improvement of the genital arousal response.

More recently, *in vitro* contractility studies, performed on noradrenaline pre-contracted vaginal strips obtained from Sprague Dawley rats according to a similar experimental model, showed that testosterone improves the NO-mediated smooth muscle vaginal cell relaxation, confirming its role in maintaining a functional muscular relaxant machinery [14]. Furthermore, the previous authors have recently focused on the RhoA–ROCK contractility pathway in the vagina, demonstrating that ROCK inhibitor Y-27632 induced a dose-dependent relaxation of noradrenaline pre-contracted vaginal strips, decreased by ovariectomy and restored by estradiol, whereas testosterone and testosterone + letrozole decreased it below the ovariectomy level [17]. These apparently conflicting data were explained by western blot analysis as a result of a reduction of RhoA activation induced by testosterone, and thus a functional, non-genomic effect of AR activation. In addition to this, the abolition of NO formation via l-NAME, a nitric oxide synthase (NOS) inhibitor, increased Y-27632 responsiveness in the testosterone group, thus supporting the hypothesis of activation of the NO pathway by the AR [17].

Compelling evidence about a potential anti-inflammatory role of androgens in the vagina is also emerging. In human vaginal smooth muscle cells (hvSMCs) isolated from perimenopausal women undergoing surgery for benign gynecological conditions, messenger RNA (mRNA) expression analysis showed that AR was the most highly expressed in hvSMCs, compared to ERα, ERβ, G-protein-coupled estrogen receptor 1 (GPER1) and progesterone receptor (PR). More interestingly, analysis of the membrane antigenic profile revealed the expression of a wide range of Toll-like receptors (TLRs), suggesting that vaginal muscle cells, although 'non-professional' antigen-presenting cells, own the potential to elicit and maintain a pro-inflammatory response. hvSMC pretreatment with DHT, a selective AR agonist, significantly decreased the mRNA expression of numerous pro-inflammatory mediators (e.g. cyclooxygenase-2 [COX2], interleukin-6 [IL-6], IL-12 and interferon-γ [IFN-γ]) induced by lipopolysaccharide (LPS), a membrane component of Gram-negative bacteria and an agonist of TLRs. This effect was significantly reduced by the AR antagonist bicalutamide [15]. Similar results were obtained by analysis of gene expression of various pro-inflammatory factors; of notable interest is the inhibition, following pretreatment with DHT, of the mRNA expression of inflammatory mediators induced by IFN-γ, a fundamental inflammatory cytokine of the T-helper 1 immune response and of chronic inflammation [15]. Therefore, AR activation is capable of suppressing the inflammatory response in hvSMCs, reducing their possibility of being involved in the initiation and maintenance of inflammation, thus representing the target of possible therapeutic strategies in numerous conditions affecting the

female urogenital system, causing chronic pain and a dramatic negative impact on the quality of life, including GSM.

All of the aforementioned evidence about the role of androgens in the vagina plays a more relevant role in view of the novel concept of 'intracrinology'. Bertin et al. first demonstrated the presence of the enzymatic pathway responsible for androgen formation as well as AR both in the epithelium and muscularis layers of the vagina in the cynomolgus monkey (*Macaca fascicularis*), the closest animal model to the human [18].

In human distal vaginal tissue samples, the enzymes involved in the reactions upstream of steroidogenesis (steroidogenic acute regulatory protein [STAR], cytochrome P450 11A1 [CYP11A1], CYP17A1) were found to be expressed at much lower levels than in the ovarian tissue [19]. Conversely, the expression of pro-androgenic steroidogenic enzymes such as 17β-hydroxysteroid dehydrogenase type 3 (HSD17β3), 17β-hydroxysteroid dehydrogenase type 5 (HSD17β5) and the three isoforms of 5α-reductase (SRD5A1, SRD5A2 and SRD5A3), implicated in the transformation of testosterone into its most active metabolite, DHT, showed a markedly higher level of expression in the distal vagina than in the ovary [19]. Moreover, mass spectrometry studies revealed a significant increase in androstenedione, testosterone and DHT in the culture medium of hvSMCs, after treatment with increasing concentrations of DHEA, therefore leading to the innovative concept that vaginal muscle cells express the enzymatic machinery necessary to produce the most active metabolites of androgens [19].

Genitourinary syndrome of menopause/ vulvovaginal atrophy: definition and epidemiology

GSM is a new definition that was proposed in 2014 to describe, in a more accurate and inclusive way, the signs and symptoms related to estrogen deficiency in the whole female genitourinary tract, including the labia, introitus, vagina, clitoris, bladder and urethra [20]. The previous terminology, 'vulvovaginal atrophy', has been considered inadequate not only because of the negative connotations of the word 'atrophy', but also given the need to go beyond the appearance of the vulva and vagina, including also a reference to the symptoms associated with the lower urinary tract [20]. The syndrome is characterized by the occurrence of genital symptoms (vaginal dryness, irritation, burning, itching and bleeding), sexual symptoms (such as dyspareunia) and/or urinary symptoms (dysuria, frequency, urgency or recurrent urinary infections) [21].

In the literature, the prevalence of GSM-related symptoms in postmenopausal women ranges from 13% to 87% [22]. Due to the underreporting of patients and physicians' unawareness, GSM has been underdiagnosed over the past decades [23]. Moreover, physical findings are only weakly correlated with reported symptoms [24].

Contrary to vasomotor symptoms, GSM is a condition that progresses with time, increasing in frequency and intensity 5 years from menopause compared to 1 year postmenopause, and impacting heavily on quality of life. In particular, in sexually active women, pain during intercourse is often reported as the most bothersome manifestation of GSM, importantly affecting sexual satisfaction [23,25].

When collecting a patient's history, a crucial point is to consider the exposure to potential vulvar irritants (i.e. tight-fitting clothing, synthetic underwear, scented detergents or dyed toilet paper) and to investigate the use of medications, history of previous surgery and the presence of other medical conditions [26].

Genital examination validates clinical diagnosis of VVA. The degeneration of connective tissue and the decrease in number of epithelial layers consequent to hypoestrogenism cause a reduction in elasticity and moisture with thinning of vaginal rugae. Vulvovaginal mucosa usually appears pale and dry or erythematous with petechiae and, in severe cases, shrinkage of the labia minora and of the introitus can be observed. Pelvic organ prolapse such as that of the uterus or the vaginal vault, cystocele and rectocele are also included among the possible manifestations of the GSM [20].

Subjective assessment tools can be employed to quantify the severity of GSM symptoms and measure the improvement after treatment. For example, the Vulvovaginal Symptoms Questionnaire and the Day-to-Day Impact of Vaginal Aging Questionnaire have recently been validated [27].

Regarding the evaluation of GSM signs, measurement of vaginal pH can be incorporated into the vaginal health index, together with the four other parameters (vaginal elasticity, vaginal secretions, epithelial mucous membrane and vaginal hydration), to diminish intra-operator variability. Since the reduction of glycogen production from vaginal epithelial cells occurring during hypoestrogenism leads to a decrease in lactobacilli populations and their lactic acid production, a vaginal pH higher than 4.5 is indicative of VVA [28,29]. Additionally, the Vaginal Maturation Index is an objective measure that calculates the relative proportion of parabasal, intermediate and superficial vaginal epithelial cell types in a cytology sample, being suggestive for VVA when lower than 5% [30].

Laboratory testing or biopsies are usually not required, but they can be useful in the differential diagnosis when appearance is atypical or the lesion is unresponsive to treatment [31]. It is indeed essential to differentiate VVA from other vaginal conditions such as vaginal lichen sclerosus and planus, contact dermatitis and vulvar cancer, as well as to rule out vaginal or sexually transmitted infections [32].

Local estrogens represent an effective therapeutic strategy in women with GSM when vasomotor symptoms are not the primary concern. Although systemic absorption is minimal, when treating breast cancer patients it is recommended to discuss risks and benefits with the treating oncologist [33]. In the presence of such contraindications, women with dyspareunia can benefit from the application of non-hormonal vaginal moisturizers together with using water, silicon or oil-based lubricants to reduce sexual friction. Further emerging non-hormonal strategies to address GSM include pelvic floor muscle training and energy based devices such as the vaginal laser [34,35]. Ospemifene, a selective ER modulator, is an oral medication approved by medical authorities that can be prescribed in women unable or unwilling to use local

estrogens, although the short-term risk of inducing hot flushes must be considered [36].

A new perspective in the treatment of GSM: androgens

In view of the aforementioned emerging evidence, the vagina appears as a target organ for androgens, which through the activation of the AR can reduce local inflammation and maintain its contractile/relaxant machinery, but also as an endocrine organ, with the ability to synthesize more potent androgens from their precursors (e.g. DHT from DHEA).

DHEA

DHEA is a weak androgen mainly secreted by the adrenal gland, and to a lesser extent by the ovary. It seems to have both local and systemic effects, and its plasma level tends to decrease with age, as occurs for estrogens and testosterone.

In 2016 prasterone, a synthetic equivalent of DHEA, was approved by the US Food and Drug Administration (FDA) and successively by the European Medicines Agency (EMA) for the treatment of moderate to severe symptoms of VVA in menopausal women. It is administered in the form of a vaginal suppository (dose 6.5 mg, concentration 0.50%) once daily at bedtime.

In order to examine the dose and scheduling of once-daily intravaginal prasterone, five randomized, multicenter, double-blind, phase 3 studies involving more than 1500 menopausal women were conducted. In two reference phase 3 pivotal RCTs among these ($n = 255$ and $n = 588$, respectively), prasterone treatment was associated with a significant difference in superficial cells, parabasal cells and vaginal pH as well as with a significant improvement in dyspareunia from baseline [37,38]. Noteworthy, in a phase 3 placebo-controlled RCT enrolling 464 gynecological or breast cancer survivors, patients who received 6.5 mg intravaginal prasterone showed a significant increase in sexual function after 52 weeks of therapy; moreover, testosterone, estradiol and DHEAS circulating levels were significantly higher, but remaining within the normal menopausal range [39]. Similar results were observed in a phase 1/2 RCT, placebo-controlled, double-blind study in postmenopausal women ($n = 40$) receiving daily prasterone (0.5%, 1.0% or 1.8%) or placebo. After 7 days of treatment, serum levels of estradiol and testosterone remained within the values found in normal postmenopausal women for the 0.5% and 1.0% doses [40]. Finally, these safety data were confirmed by a pooled analysis of the principle phase 3 studies ($n = 723$) [41].

Furthermore, a more recent pilot study including 10 breast cancer survivors receiving aromatase inhibitors reported that treatment with local DHEA (one ovule/day for 1 months, then one ovule every two nights for the following 5 months) was associated with a significant improvement in the visual analog scale of dyspareunia score (from 8.5 to 0.4, $p = 0.0178$), the vaginal health index scale (from 9.75 to 15.8, $p = 0.0277$) and the Female Sexual Function Index score (from 11.2 to 20.6, $p = 0.0277$), with serum estradiol remaining at low levels (from 3.4 to 4.3 pg/ml, $p = 0.9136$), and thus in the safety range [42].

In all clinical trials investigating possible adverse effects of prasterone, the most common was vaginal discharge (5.72% of women treated reporting vaginal discharge vs. 3.55% in the placebo group in the four 12-week trials; 14.2% of women reporting vaginal discharge in the 52-week trial) [43]. The 52-week open-label trial also showed an adverse effect of abnormal Pap smears in 11 out of 521 women, 10 reporting atypical cells of undetermined significance and one reporting low-grade squamous intraepithelial lesions [44]. Trials examining the endometrial safety of intravaginal prasterone showed atrophic or inactive endometrium in all women [37,45].

Since to date there are no head-to-head trials of prasterone versus vaginal estrogens, and cross-trial comparisons present limitations, a 2017 review of phase 3 trials compared the effect of daily administration of intravaginal DHEA 6.5 mg (0.5%) for 12 weeks versus estrogen equine conjugates 0.3 mg versus estradiol 10 µg in women complaining of VVA. The authors concluded that prasterone was at least as efficacious as the comparators, with clearly positive effects on the symptoms and pathological mechanisms of VVA, in the absence of systemic exposure, consistent with the principles of intracrinology [46].

A recent meta-analysis exploring the efficacy of vaginal therapies alternative to vaginal estrogens on sexual function and orgasm of menopausal women confirmed a statistically significant difference in favor of 0.5% DHEA over placebo for dyspareunia and vaginal dryness, whereas orgasmic function was the same for the 0.5% DHEA and placebo [47]. Further data regarding efficacy on female sexual dysfunction were collected by tools other than validated female sexual dysfunction questionnaires, because of inconsistent/missing data, but DHEA presented a statistically significant advantage over placebo also in the improvement of sexual function [47].

Summarizing, the real potential of prasterone is represented by its positive local effects on VVA symptoms as well as its beneficial effects on sexuality and dyspareunia, in the absence of a significant systemic absorption, so it currently represents a safe and innovative therapeutic opportunity in the treatment of VVA. However, it has been claimed that the studies evaluating the efficacy of prasterone show limited quality, for example due to the use of unvalidated or clinically unrelated outcome measures. For this reason, larger studies employing more accurate symptom assessment tools are needed, as well as studies investigating the long-term safety of the drug in women with a history of hormone-sensitive malignancies, who particularly could benefit from local androgen therapy [48].

Testosterone

Since female genitourinary tissue has been demonstrated to express AR, off-label testosterone topical therapies, such as compounded local creams, can also represent a therapeutic option against GSM. Interestingly, testosterone – as well as prasterone treatment are getting attention as a therapeutic option for GSM in breast cancer survivors, given their trigger

on the activation of vaginal sex steroids receptors, without activating ERs in different tissues, owing to the reduced expression of aromatase at this level [19,49].

However, clinical data on local testosterone therapy are limited. A 2018 systematic review of intravaginal testosterone for the treatment of VVA, contemplating six separate clinical trials, each enrolling from 10 to 80 participants, with either single or multiple administrations of testosterone during 4–12 weeks, suggests that intravaginal testosterone is able to reduce vaginal pH, to increase the percentage of vaginal lactobacilli and to improve the vaginal maturation index [50]. Although many of the considered studies reported an improvement in sexual function, at a critical appraisal this result seems to be inconsistent, due to the lack of a placebo group in four out of six studies and of an adjustment for baseline differences [50]. Accordingly, the aforementioned meta-analysis investigating vaginal therapies alternative to estrogens showed that sexual satisfaction and sexual function scores were not different when testosterone was compared or added to estrogen therapy [48]. Moreover, data about safety remain scarce because of the small study samples, their short durations and an inaccurate assessment of sex steroid levels [50].

The safety profile of intravaginal testosterone becomes particularly relevant when referring to cancer survivors. An updated 2022 systematic review of available evidence from randomized trials conducted in women with breast cancer concluded that intravaginal testosterone therapy was associated with a significant improvement in vaginal symptoms (e.g. pain, dryness, dyspareunia), while it was not associated with any improvement in the Female Sexual Function Index total score or with significant changes in vaginal hormone responses (e.g. as assessed by vaginal health index) [51]. However, only one study including 21 women taking testosterone met the inclusion criteria for the systematic review [51,52].

Androstenedione

As a steroid prohormone and an intermediate in the synthetic pathway of androgens and estrogens, androstenedione could theoretically represent a therapeutic strategy against GSM. It can be administered as an oral formulation; however, scarce evidence is available regarding its safety and its impact on sexual function. In a small study published in 2002, 30 healthy postmenopausal women randomly took a single oral dose of 50 mg or 100 mg androstenedione or placebo [53]. The authors concluded that both androstenedione doses were able to significantly increase testosterone and estrone, but not estradiol serum levels in the treated groups, with peak testosterone levels higher than the normal upper limit in 4/10 patients in the 50 mg group and 6/10 in the 100 mg group [53]. Consequently, longer-term data, safety and efficacy profiles of androstenedione treatment are needed.

Conclusions

Estrogens have been traditionally considered the primary hormones that act on vaginal tissue to maintain its health and function. Although estrogens exert a crucial role, current research indicates that the human vagina is also an androgen-target organ, and it owns the ability to synthesize androgens. Given the lack of testosterone-based products approved by regulatory agencies to treat VVA and the other symptoms of GSM, the possibility of using prasterone, which works by providing a local source of DHEA to the vaginal tissues, appears to be a targeted treatment, adding a novel physiological androgenic component to local therapy.

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