Practical Aspects in the Management of Vaginal Atrophy and Sexual Dysfunction in Perimenopausal and Postmenopausal Women

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ABSTRACT

Introduction. The decline in circulating estrogen levels in peri- and postmenopause has a wide range of physiological effects, including atrophy of tissues in the urogenital tract. Vaginal atrophy is an important contributor to postmenopausal sexual dysfunction.

Aim. To provide a framework for clinical evaluation and clinical management of sexual dysfunction secondary to vaginal atrophy.

Method. Conduct a brief overview of literature on evaluation and treatment of vaginal atrophy, augmented with the authors’ clinical observations and experience.

Results. Estrogen decline disrupts many physiological responses characteristic of sexual arousal, including smooth muscle relaxation, vasocongestion, and vaginal lubrication; genital tissues depend on continued estrogen and androgen stimulation for normal function. An upward shift in vaginal pH as the result of vaginal atrophy alters the normal vaginal flora. Reduced lubrication capability and reduced tissue elasticity, in addition to shortening and narrowing of the vaginal vault, can lead to painful and/or unpleasant intercourse. At the same time, diminished sensory response may reduce orgasmic intensity. Other contributors to peri- and postmenopausal sexual dysfunction include reduced androgen levels, aging of multiple body systems, and side-effects of medications. Workup of sexual health problems starts by taking a comprehensive sexual, medical, and psychosocial history, followed by complete physical examination and laboratory evaluation. Clinical management includes measures to preserve and enhance overall health, adjustment of medication regimes to reduce or avoid side-effects, and topical or systemic hormone supplementation with estrogens and/or androgens.

Conclusions. No single therapeutic approach is appropriate for every woman with peri- or postmenopausal sexual dysfunction; instead, treatment should be based on a comprehensive evaluation and consideration of medical and psychosocial contributors to the individual’s dysfunction. Further research is required to establish optimal regimens of hormonal and nonhormonal agents, including dosages/dosage forms and duration of treatment, for specific subtypes of sexual dysfunction. Goldstein I, and Alexander JL. Practical aspects in the management of vaginal atrophy and sexual dysfunction in perimenopausal and postmenopausal women. J Sex Med 2005;2(suppl 3):154–165.

Key Words. Postmenopause; Management; Vaginal Atrophy; Sexual Dysfunction

Introduction: Women’s Sexual Health Problems in Peri- and Postmenopause

Women in the perimenopausal and postmenopausal years frequently encounter a range of new medical issues such as coronary heart disease and osteoporotic fractures as well as sexual health concerns [1]. Although quality of life is not negatively impacted as the result of sexual dysfunction for some women or their partners, for other women, sexual problems can be associated with significant personal distress and may result in diminution of their ego, self-worth, and self-esteem, as well as a significant reduction in life satisfaction and quality of the couple’s relationship [2,3].

Sexual dysfunctions in younger women are often reversible or situational. Women frequently experience episodes of decreased desire, arousal, and orgasmic functioning during the postpartum period or while breast-feeding; during periods of relationship discord; or in response to a range of
other stressors. During peri- and postmenopause, however, sexual dysfunctions occur more frequently, are more often irreversible, and are more likely to be progressive, particularly if the pathophysiology of the dysfunction is related to vaginal atrophy secondary to estrogen deficiency [4]. The consequences of hormonal insufficiency may not be reversible unless local or systemic estrogen treatment is initiated, and hormonal insufficiency is not a condition that decreases in intensity over time [5–8].

Peri- and postmenopausal women may not complain of sexual problems or even broach the subject of their sexual function with health-care providers. Many women believe their sexual function is too personal, too private, and too “off limits to outsiders” to discuss. This may be so even if the woman is experiencing significant distress as a result of her sexual health concern, and even if the discussion would be with a close friend [9].

It is thus very important for health-care professionals who treat women with general health concerns to initiate direct discussion of sexual function with peri- and postmenopausal women. Providers who are uncomfortable addressing the topic of women’s sexual health during the routine office visit should consider receiving postgraduate training on evidence-based management principles for woman’s sexual health concerns (available from the International Society for the Study of Woman’s Sexual Health [http://www.isswsf.org]). Armed with such knowledge, health-care professionals may be more amenable to discuss basic and initial management principles with their patients who have sexual health concerns [6,9].

Contemporary health-care professionals who treat aging patients may be more at ease with dialog about sexual health, especially in the era of safe and effective treatments for erectile dysfunction [10]. The availability of selective phosphodiesterase type 5 (PDE5) inhibitors, however, may be viewed as a double-edged sword. These medications have empowered some women distressed by their sexual health problems to seek help from these same health-care professionals, only to be confronted with the lack of consensus regarding appropriate treatment. Other women have been challenged by the return of their partners’ sexual functioning and resumption of sexual intercourse in light of their own urogenital aging and associated physical problems. Consequently, some experts recommend that the female partner be evaluated and treated, if necessary, for symptoms of urogenital atrophy, sexual dysfunction, and personal distress, concurrent with the treatment of the male partner with erectile dysfunction by PDE5 inhibitors [11]. One useful strategy for health-care professionals who provide medical care to women is to introduce sexual health issues during the routine, annual pelvic examination, especially if vaginal atrophy is identified [12,13].

The onset of sexual health problems in women during the peri- and postmenopausal years does not necessarily mean that their sexual function should be considered over. The goal of this article is to provide an evidence-based overview of the epidemiology, pathophysiology, and management of sexual dysfunction associated with vaginal atrophy. We have focused on this area because vaginal atrophy underlies many of the physical aspects of sexual problems associated with menopause and can frequently lead to the development of secondary psychological contributors to sexual dysfunction. Our interest in the recognition and treatment of vaginal atrophy and associated conditions is predicated upon the belief that sexual health is a fundamental human right and an integral part of a healthy life.

It should be emphasized that a woman’s sexual response is a complex interactive process involving a unique set of mind, body, and partner issues. It is important to understand that successful treatment of vaginal atrophy may not correct dyspareunia, low interest, diminished arousal, and muted orgasm if the woman being treated is depressed or living with a violent partner, or is the primary caregiver to a child with a chronic medical condition (to give but a few examples). All contributors to woman’s sexual health, not only hormonal ones, should be evaluated when considering therapeutic approach [9].

Normal Genital Physiology

Peripheral genital sexual stimulation results in a series of physiological changes, especially relaxation of smooth muscles in the genital tissues, including the vagina, clitoris, corpus spongiosum, Skene’s glands, minor and major vestibular glands, and other structures. Sexually stimulated genital smooth muscle relaxation results in genital vasocongestion, tissue engorgement, increased genital blood flow, and increased genital lubrication. In addition, smooth muscle relaxation causes the vaginal canal to increase in length and width and the vaginal lamina propria to engorge, while a plasma transudate appears as droplets on the vaginal epithelial surface. The labia increase in size and
receive lubricant from minor and major vestibular glands, while the clitoral glands, shaft, and crus engorge and the angle between the glans and the vestibule widens. The corpora spongiosa receive increased blood flow, resulting in engorgement of these erectile tissues [14]. The ability of urogenital tissues to undergo and sustain these physiological changes has been shown to be strongly dependent on the steroid hormonal milieu, especially the level of estradiol [7,14].

**Role of Sex Steroid Hormone Deficiencies in Peri- and Postmenopausal Sexual Dysfunction**

**Diminished Estrogen Levels**

Menopause is characterized by a cessation of ovarian estradiol production. Although some residual peripheral estrogen production remains through conversion of androstenedione to estrone, as well as aromatization of androgens into estrogens in adipose tissue, estrogen levels decline precipitously during the menopausal transition [15].

Estrogens are required for normal genital tissue structure and function; their action is mediated by estrogen receptors present in the epithelial cells, endothelial cells, and smooth muscle cells of genital tissues. The high level of estrogen receptors found in the vagina, vulva, vestibule, labia, and urethra suggests that these genital tissues require estrogen for structure and function; diminished estrogen production renders these genital tissues highly susceptible to atrophy. Atrophic changes can be identified after weeks to months of exposure to reduced estrogen levels [7,14].

Vaginal atrophy secondary to estrogen decline is a key contributor to sexual dysfunction [12,13,16,17]. One consequence of vaginal atrophy is an alteration of the acidic vaginal pH that discourages growth of pathogenic bacteria. In an estrogen-rich environment, the normal vaginal flora hydrolyze glycogen from sloughed epithelial cells into glucose, which is then metabolized to lactic acid. In postmenopausal women, epithelial thinning reduces the glycogen available for this process. The resulting change to neutral or alkaline pH leads to a shift in the vaginal flora, increasing the likelihood of vaginal discharge and odor [18].

Atrophy of vaginal epithelial, vascular, muscular, and connective tissue causes the vaginal vault to pale or become colorless, with loss of the multiple folds or rugae that are present in the estrogenized vagina. Atrophy of the lamina propria blood vessels diminishes blood flow to the tissues, resulting in decreased lubrication and vaginal dryness; the degree of vaginal dryness becomes more severe with increasing time since menopause [19]. Thinning of the epithelial layer leads to increased friability and lowered elasticity of vaginal tissues. When coital activity is attempted under conditions of estrogen deficiency, marked shortening and narrowing of the vaginal vault, in addition to reduced lubrication and elasticity, can make sexual activity painful, unpleasant, and unsatisfactory [1,20].

Estrogen deficiency may also result in reduced vestibular sensation, with diminished perception of vibratory and hot and cold stimuli. The attenuation of vestibular sensation may be a contributor to diminished and muffled orgasmic intensity [21]. Persistent estrogen deficiency and resulting reduced blood flow also adversely affect other urogenital tissues. The clitoral hood may become phimotic and the glans clitoris may atrophy and become fibrosed. Other changes include thinning of the hair of the mons and atrophy and shrinkage of the labia minora and labia majora with decreased subcutaneous fat and skin elasticity; it is common for women to experience itching as these tissues atrophy. The endocervical glandular tissue produces less mucin, further contributing to vaginal dryness. Estrogen deficiency also adversely affects the bladder; women frequently complain of dysuria, increased urinary frequency, urgency, incontinence, and postcoital urinary tract infections [7,14].

There is a strong correlation between low estradiol levels, vaginal atrophy, and dyspareunia. Compared with women with serum estradiol levels above 50 pg/mL, significantly more women with estradiol levels less than 50 pg/mL report vaginal dryness, dyspareunia, and pain during sexual activity. In addition, diminished coital activity has been associated with estradiol levels below 35 pg/mL [22].

The development of vaginal atrophy, vaginal dryness, and dyspareunia frequently leads to avoidance of sexual intercourse secondary to the fear of painful intercourse. In addition, estrogen deficiency may further prolong the time to achieve vaginal vasocongestion, resulting in inadequate vaginal lubrication and reduced intensity and number of vaginal and uterine contractions during orgasm. Low frequency of sexual activity can in turn lead to further vaginal atrophy, exacerbating dyspareunia and ultimately triggering a vicious cycle of avoidance, performance anxiety, and decreased sexual desire [6,10].
**Diminished Androgen Levels**

Androgens are critical in maintaining genital tissue structure and function in women. They also contribute to other sexual and nonsexual physiological functions, including desire and orgasm responses, bone and skeletal muscle metabolism, cognition, feelings of well-being, and improved mood. Low androgen levels frequently lead to classic complaints of decreased libido and impaired sexual functioning, but may also induce muscle wasting, osteoporosis, loss of energy, changes in mood, and depression [23,24].

Androgens are synthesized in the ovaries and zona reticularis of the adrenal gland from cholesterol and in the periphery from dehydroepiandrosterone. Dehydroepiandrosterone, androstenedione, total and free testosterone levels start to decline in the early 40s in women and continue to decrease with advancing age. During pre- and perimenopause, most of this decline is the result of reduced adrenal synthesis; although adrenal production continues to fall, most of the postmenopausal decline is due to ovarian failure. In addition, levels of sex hormone-binding globulin (SHBG), which reduces testosterone bioavailability because of its high binding affinity, increase in postmenopausal women, especially those treated with oral estrogen therapy. The combination of reduced androgen synthesis and increased androgen sequestration by SHBG results in a reduction in free testosterone [6,7].

**Role of Concomitant Medical/Surgical Conditions**

Medical and surgical conditions and use of nonpsychiatric prescriptions can occur at any time in a woman’s life but are predictably more common with increasing age. Women in peri- and postmenopause are therefore subjected to alterations of pertinent biological factors beyond the integrity of their sex steroid hormonal milieu. Healthy sexual function depends on the integrity of neurological and vascular systems. Age-related changes in these systems can profoundly affect sexual health. Postmenopausal women frequently confront the onset of new cardiovascular risk factors, including metabolic syndrome, diabetes mellitus, dyslipidemia, hypertension, and increased body mass index. In addition to increasing the risk of angina, cerebrovascular accident, and myocardial infarction, these conditions may require the initiation of multiple cardiovascular prescription medications. Neurological conditions such as multiple sclerosis, Parkinson’s disease, and diabetic neuropathy are also more prevalent in postmenopause.

Other medical conditions, such as arthritis, become more prevalent with aging, and may adversely affect sexual function, especially interest, arousal, and orgasm capabilities. Nonsteroid endocrine hormonal dysfunctions, such as hypothyroidism, also become more frequent with increasing age. Subclinical hypothyroidism is associated with reduced health status as well as mood and bone metabolic changes [25].

Prescription medications for nonpsychotropic indications, such as antihistamines or antihypertensive medications, may adversely affect libido, arousal, and/or orgasm response. Specifically, in peri- and postmenopausal women with vaginal atrophy, the concomitant use of agents that dry mucus membranes may significantly worsen dyspareunia secondary to reduced lubrication capability [7].

The high incidence of mood and anxiety disorders in peri- and postmenopausal women is associated with increased use of prescription drugs that affect the central nervous system, such as selective serotonin reuptake inhibitors (SSRIs). The introduction of SSRIs was followed by the consistent observation that in some patients they have an adverse impact on orgasm and/or a decline in libido [26–28]. Antidepressant-associated sexual dysfunction (AASD) is typically observed soon after treatment initiation, and its course is highly variable; the estimated frequency of AASD ranges from 14% to 73% [29]. Some patients experience only mild impairment, while others have significant loss of orgasm or libido; these side-effects improve for some and persist for others. AASD has important implications for successful treatment of the large population of woman with depression. Side-effects are a principal reason for discontinuing antidepressants, with sexual dysfunction the primary cause in many cases [30].

The diagnosis of AASD is confounded by the fact that many women have orgasm and libido problems related to their major affective disorder and may also have female sexual dysfunction (FSD) resulting from menopausal changes to the urogenital tract. The dynamic relationship between these conditions can be extremely complicated; multiple conditions may require serial or concurrent treatment to effect improvement in FSD. Improvement in their major affective disorder may result in resolution of their “appetitive” problems in the sexual realm but then be confounded by the occurrence of AASD [27,31–33].
Unfortunately, to date most studies of AASD and its relationship to other sexual dysfunctions have been observational rather than prospective, and have therefore been poorly controlled with regard to pre-existing and contemporaneous variables [34]. Many patients experience some degree of relief from their sexual side-effects when the clinician diligently assesses pre-existing functioning, observes for new onset of FSD, and then changes medications or uses some of the established augmentation strategies for amelioration of the AASD. Although more research is needed the use of PDE5 inhibitors may be an addition to these augmentation strategies. Currently, the more traditional approach has been to shift treatment (when medically feasible) to bupropion or buspirone [34–36].

Women in peri- and postmenopause are also more likely than younger women to require surgical procedures that affect their breasts, uterus, and/or ovaries, any of which may directly or indirectly adversely affect sexual function as well as sexual self-esteem and self-image. In addition, nongenital surgery, such as coronary artery bypass surgery, can lead to temporary or prolonged physical and emotional distress that may affect sexual function. It is important for the postmenopausal woman and her partner to be offered preoperative counseling with regard to potential adverse sexual changes that might follow genital and nongenital surgical intervention [7].

Clinical Evaluation of Women’s Sexual Health Problems in Peri- and Postmenopause

History and Physical Examination

Sexual, Medical, and Psychosocial History-Taking

A complete history and physical examination should be the basis of any evaluation of sexual health problems. The history should include sexual, medical, and psychosocial aspects, so that all potential factors contributing to the sexual health difficulty can be characterized. In addition, for patients with sexual health concerns, consideration should be given to a psychological interview and to obtaining certain laboratory testing procedures [9].

The sexual history should evaluate the woman’s current sexual functioning in terms of interest, arousal, and orgasm, in comparison with her peak reproductive years. Peri- and postmenopausal women should be assessed for the degree of discomfort, tenderness, soreness, or pain involved with sexual activity. Attempts to localize the origin of pain on schematic diagrams of the woman’s genitalia may be helpful.

The use of a validated, reliable standardized self-administered questionnaire (SAQ) may provide a productive starting point to identify the possible presence of a sexual problem and to classify the problem as a disorder of desire, arousal, or orgasm, and/or a problem of sexual pain. SAQs are valuable screening tools that are easy to administer and score and have normative values for populations of women with and without sexual dysfunction. Commonly used instruments include the Female Sexual Function Index and the Sexual Function Questionnaire (see the article by Althof et al. in this supplement). It is also important to understand the limitations of SAQs for clinical diagnosis. Determination of specific psychological contributors or confounds, contextual conditions, and other features and characteristics of physical and psychological health associated with each woman’s unique sexual concerns typically requires more traditional assessment, through structured history and physical examination [4,9].

The medical history should evaluate for symptoms of estrogen deficiency such as vaginal dryness, vaginal bleeding with minimal sexual contact, pain and soreness after sexual activity, hot flashes, and night sweats. Assessment should also include medication use, including over-the-counter and prescription drugs, as well as any drugs of abuse [9].

The psychosocial history should assess such issues as social factors, past sexual beliefs, past sexual abuse and trauma, emotional concerns, and interpersonal relationship matters. Any history of mood or psychiatric disorders should always be identified [9].

Physical Examination

A pelvic examination is an essential component in the workup of the menopausal woman with sexual health complaints. During this examination, the presence or absence of vaginal atrophy should be assessed. Classic findings suggesting atrophy include dryness, thinning, pale color, loss of rugae, lack of shiny vaginal secretions, sites of trauma in the vestibule and vagina, atrophy of the labia, reduced pelvic floor skeletal muscle tone, and pain-triggering spots. It may be helpful to have the patient observe the atrophic changes using a mirror or a digital camera, if the patient is amenable. Figures 1 and 2 illustrate, respectively, a healthy vestibule during reproductive years, and vestibules during various stages of postmenopausal vestibular atrophy.
A vaginal pH above 5 is consistent with vaginal atrophy, especially if the elevated pH cannot be attributed to the presence of an infective agent. The astute clinician should also perform a complete physical to rule out other comorbid conditions that might be causing sexual dysfunction (such as a thyroid goiter) [9].

**Laboratory Testing**

In contrast to the consensus supporting the need for a detailed history and physical examination, there is no current consensus on what laboratory testing should be considered for peri- and postmenopausal women with sexual health concerns [9].

If the physician believes that an endocrine evaluation is relevant to establish the diagnosis and to establish a baseline prior to hormone therapy intervention, it is helpful to obtain levels of dehydroepiandrosterone-sulfate, androstenedione, free testosterone, total testosterone, SHBG, dehydrotestosterone, estradiol, estrone, progesterone, follicle-stimulating hormone, luteinizing hormone, prolactin, and thyroid-stimulating hormone. Once treatment is started, the physician should carefully consider appropriate follow-up blood tests as well as the optimal interval between tests. It is routine practice to assess dehydroepiandrosterone-sulfate, free testosterone, total testosterone, SHBG, estradiol, and progesterone hormone levels at 3-month intervals [5,6].

Similarly, if the physician believes that genital sensation and genital blood flow should be evaluated to establish the diagnosis and establish a pretreatment baseline, several tests may be considered. Assessment of genital sensation may involve measurement of vibration (biothesiometry) and/or temperature perception threshold values. Duplex Doppler ultrasonography can be used to assess genital blood flow by recording clitoral peak systolic velocities and end-diastolic velocities before and after audio-visual-mechanical sexual stimulation [9].

**Clinical Management of Women’s Sexual Health Problems in Peri- and Postmenopause**

The goal of the detailed history, physical examination, and, if appropriate, psychological interview and laboratory testing is to provide an accurate assessment of the multiple contributing factors to the sexual problem, especially the presence or absence of vaginal atrophy. An optimal management plan can then be discussed with the patient and her partner, especially if personal...
distress is an important component of the sexual problem [9].

Figure 3 depicts schematically the approach to evaluation and treatment of sexual dysfunction in postmenopausal women that is discussed here.

**Education of the Patient and the Partner**

Treatment plans should always be based on patient/partner education covering basic facts of women’s sexual health, especially the critical relationships between mind, body, and partner factors. A team approach engaging psychologically focused and medically focused health-care professionals can be especially useful. Educational topics usually include basic information on genital anatomy and genital physiology following sexual stimulation, especially vaginal engorgement, lubrication, and changes in vaginal vault dimensions. The relation between genital structural health and genital endocrinology should also be reviewed.
Nonpharmacological Modification of Reversible Causes

Because sexual health mirrors overall psychological and biological health, peri- and postmenopausal women should practice a lifestyle that optimizes both of these health domains. Simple measures, such as spending more quality time with the partner, increasing tactile stimulation, hand-holding, caressing, and discussing sexual likes and dislikes all help improve overall intimacy. On the physical side, regular aerobic exercise, appropriate hydration and diet, avoidance of nonprescription drug dependencies (nicotine, ethanol, etc.), and effective management of all reversible psychological and medical problems are essential. It is important to evaluate and review all medications that may have an adverse influence on sexual function, consulting, if appropriate, with the health-care professional who prescribed the medication. Constructive psychological and physical lifestyle changes may positively affect sexual health by enhancing well-being, self-worth, and body image, increasing overall stamina, and avoiding depression.

Hormonal Therapy

It is important to emphasize that no single type of hormonal intervention or regimen will be effective in all peri- and postmenopausal women with sexual dysfunction, even when the dysfunction is clearly secondary to hormone deficiency. Only after rigorous examination and accurate diagnosis is it possible to arrive at a hormonal supplementation strategy that is likely to improve the dysfunction.

Figure 3 Evaluation and treatment of sexual dysfunction in postmenopausal women. This figure illustrates schematically the approach to evaluation and treatment of sexual health complaints in postmenopausal women discussed in the text.

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The results of the Women’s Health Initiative Study, as well as other studies of hormonal supplementation, have led to a re-evaluation of the options available for health maintenance in postmenopausal women. Consensus guidelines developed by the North American Menopause Society suggest that hormone replacement therapy not be used for long-term disease prevention; however, shorter-term therapy for relief of menopausal symptoms remains acceptable. The guidelines further state: “Use of [estrogen therapy and estrogen/progestogen therapy] should be consistent with treatment goals, benefits, and risks for the individual woman, taking into account symptoms and domains (e.g., sexuality, sleep) that may have an impact on quality of life” [37].

**Estrogen Therapy**

Estrogen depletion is the definitive feature of peri- and postmenopause. Clinical symptoms of estrogen deficiency may include vaginal atrophy, vaginal dryness, diminished vaginal sensation, painful intercourse, and vaginal bleeding following minimal trauma. In addition, low estrogen is responsible for the classic menopausal symptoms of hot flushes, night sweats, and nocturnal awakening [1,5,6,12,13,20,22,38,39].

The use of systemic and/or localized estrogen must be individualized to each patient’s desires, requirements, and expectations. Clinicians should always consider product-specific contraindications and precautions prior to treatment initiation, and follow recommendations for patient follow-up and monitoring. Systemic estrogen therapy can successfully improve hot flushes, night sweats, and sleep disturbances that negatively affect body image, mood, and sexual desire; in women with an intact uterus, systemic estrogen should always be opposed by a progestogen [37]. Topical estrogen therapy can successfully improve vaginal lubrication and reduce dryness and dyspareunia [22,39,40]. Alleviation of such symptoms by systemic and/or localized estrogen can increase quality of life, desire, arousal, and orgasmic function [23,24].

**Systemic Estrogen Therapy and Vaginal Atrophy**

Several clinical trials have shown that the distressing symptoms of vaginal atrophy associated with low estrogen states are ameliorated following estrogen therapy [23]. Low doses of systemic conjugated equine estrogen, with and without medroxyprogesterone acetate, reduced vaginal atrophy compared with placebo in several thousand healthy menopausal women [16]. A randomized clinical trial found that among postmenopausal women with vaginal atrophy, a continuous low-dose estradiol-releasing vaginal ring provided comparable relief and was more acceptable than conjugated equine estrogen vaginal cream [41]. Another comparative study of menopausal women found that local 25-hydroxy,17-β estradiol vaginal tablets and conjugated equine estrogen vaginal cream were equally efficacious in relieving vaginal atrophy, but the vaginal tablets produced less endometrial proliferation than the cream [42].

The chemical form by which estrogen is delivered can also impact efficacy. One placebo-controlled trial, conducted in postmenopausal ovariectomized women with sexual dysfunction who were receiving estrogen therapy, demonstrated significant improvement in vaginal symptoms, as well as mood, sexual desire, enjoyment, and orgasmic frequency among women receiving ethinyl estradiol (50 µg/day) compared with those receiving levonorgestrel (250 µg/day), a combination of these two substances or placebo [43].

**Local Estrogen Therapy and Vaginal Atrophy**

Local estrogen therapy can effectively restore vaginal epithelium and relieve atrophy within weeks to months. There are a variety of local vaginal estrogen therapies, including creams consisting of conjugated equine estrogen, estradiol, and estriol. Several studies have shown that these local therapies effect restoration of normal vaginal cytology and improvement of vaginal atrophy and dryness. Higher-dose estrogen vaginal creams can also result in increased systemic estrogen concentrations due to absorption through mucus membranes. Other forms of local estrogen delivery systems include rings and tablets, which release hormone gradually. Typically, a 2 mg estradiol ring is placed in the vagina for 3 months, while a 25 µg estradiol tablet is delivered daily via single vaginal dose applicator for the first 2 weeks of treatment, then decreased to 1 vaginal tablet twice weekly as maintenance therapy [17].

**Androgen Therapy**

Dehydroepiandrosterone, synthesized in the ovaries and the adrenal gland, is the first androgen in the biosynthetic pathway and is thus considered the androgen precursor. A placebo-controlled study of dehydroepiandrosterone in perimenopausal women with complaints of altered mood and well-being found that active treatment produced changes in hormone levels (242% increase
in dehydroepiandrosterone, 95% increase in testosterone), but was no more effective than placebo in improving perimenopausal symptoms, mood, dysphoria, libido, cognition, memory, or sense of well-being [44].

Testosterone has been used to treat postmenopausal women for more than 50 years. Transdermal patches or gels, which are more consistently absorbed and avoid first pass through the liver, are currently being studied for safety and efficacy in reducing sexual symptoms associated with testosterone insufficiency. Recently, transdermal testosterone patches were compared with placebo in estrogenized women who had undergone oophorectomy and hysterectomy. The study results showed that the 300 mg testosterone patch was significantly more effective than the 150 mg dose or placebo in improving frequency of sexual activity, pleasure, and fantasy during a 12-week period [45].

Unfortunately, there is no consensus at this time on the optimal level of testosterone for response, nor is there consensus on the ability of pretreatment androgen levels to predict response to androgen therapy. In addition, because treatment of FSD with testosterone is currently considered off-label, safety and efficacy data are limited. Possible adverse effects of testosterone include weight gain, clitoral enlargement, increased facial hair, voice deepening, and decreases in high-density lipoprotein cholesterol, all of which are dose dependent [45].

Tibolone is a synthetic steroid that is available in Europe and Asia for the management of climacteric symptoms and the prevention of osteoporosis [46]. Recent evidence suggests that tibolone may improve mood and libido in postmenopausal women because it has androgenic as well as progestogenic and estrogenic effects. More data are needed to fully evaluate the effect of tibolone on postmenopausal women with low sexual desire.

Nonhormonal Pharmacotherapy

Oral PDE5 inhibitors, nonspecific adrenoceptor antagonists, and topical prostaglandin E1 have been used off-label as vasodilators to promote genital smooth muscle relaxation and vascular engorgement. Such agents may enhance genital engorgement and lubrication response in menopausal women; however, well-controlled, double-blind placebo-controlled safety and efficacy research data are required. Similarly, more research is needed to evaluate central agents, such as dopamine receptor antagonists and melanocyte-stimulating hormone analogs, for the treatment of women with sexual health problems [7,10].

Summary

Peri- and postmenopausal women who wish to consider treatment for sexual health problems should be offered the opportunity for safe and effective sexual health care involving a combination of psychological- and biological-focused health-care professionals. The first step is for the woman to undergo a detailed history and physical examination. Psychological issues such as mood disorders, past trauma and abuse, cultural beliefs, drug-dependency issues, interpersonal relationship concerns, partner's sexual function, and social structure assist in understanding the role that menopause plays in a woman's overall sexual health. Self-report measures of a woman's sexual function facilitate the identification of the likely presence or absence of a sexual health problem. In placebo-controlled investigations in postmenopausal women, both systemic and topical estrogen supplementation have been shown to be safe and effective for the treatment of vaginal atrophy, vaginal dryness, and dyspareunia. In placebo-controlled studies, androgen therapies have been shown to be effective for the treatment of hypoactive sexual desire disorder in postmenopausal women; they have also been shown to result in improvements in orgasm, lubrication, receptivity, and satisfaction. However, the optimal dose of testosterone supplementation remains controversial. Further research is necessary to establish safety, duration of treatment, and efficacy for systemic estrogen and testosterone replacement for the management of menopausal sexual dysfunction.

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