Key Messages

- Female sexual dysfunction (FSD) is a multidimensional problem combining biological, psychological and interpersonal elements of multiple etiologies.
- FSD can occur at any age, but is most common around middle age as a result of both normal aging and the specific hormonal changes that occur at menopause.
- Menopause-associated estrogen deprivation leads to urogenital epithelial thinning, reduced lubrication during sexual arousal and dyspareunia. Decline in testosterone levels may result in decreased libido and decreased sexual activity, and fatigue.
- In peri- and postmenopausal women, before considering other treatments specifically aimed at sexual symptoms, associated medical conditions first need to be evaluated and treated.
- Other physiological, psychological, sociocultural, interpersonal and lifestyle factors may also be important and should be addressed.
- Intervventional options for FSD include hormonal therapies such as estrogens, testosterone, combined estrogen/testosterone and tibolone.
- Non-pharmacological approaches should be used first, focusing on lifestyle and psychosexual therapy, moisturizers and lubricants.
- Symptomatic vulvovaginal atrophy (VVA) may be treated with vaginal moisturizers, lubricants, low-dose vaginal estrogen therapy.
- Hormonal therapy (HT) with estrogens alone or in combination with progestogens improves sexual function when used in women with menopausal symptoms or in early postmenopause.
- Tibolone has androgenic effects and may be first choice for women who need HT and where desire and arousal are the main problems in terms of sexual dysfunction.
- Local vaginal estrogen specifically aims at treating dryness and discomfort during intercourse and is 100% effective in VVA, with no systemic effects.
- Testosterone therapy may be helpful in carefully selected postmenopausal women with female sexual interest/arousal disorder. However, there are no laboratory tests to determine a threshold for mandatory treatment in women and there are no testosterone preparations available specifically for use in women, so using testosterone for FSD in South Africa needs to be undertaken with care.

Introduction

The International Menopause Society (IMS) defines female sexual dysfunction (FSD) as a multidimensional problem combining biological, psychological and interpersonal elements of multiple etiologies. FSD can occur at any age, but is most common around middle age as a result of both normal aging and the specific hormonal changes that occur at menopause.

Menopause-associated estrogen deprivation leads to urogenital epithelial thinning, reduced lubrication during sexual arousal and dyspareunia. Decline in testosterone levels may result in decreased libido and decreased sexual activity, and fatigue. Around menopause there are numerous medical conditions that can be associated with sexual dysfunction, including diabetes mellitus, cardiovascular disease, hypertriglyceridemia, hypertension, neurological disease, genitourinary disease and psychiatric disorders. These
Menopausal hormone therapy and sexual health

Five specific domains of sexual dysfunction may be identified in women, with considerable overlap between them (Figure 1).

**Figure 1. Domains of sexual dysfunction in women**

Sexual desire disorders  
Sexual arousal disorders  
Orgasmic disorder  
Dyspareunia  
Vaginismus

In postmenopausal women with FSD, sexual desire and sexual arousal are most affected. Dyspareunia is most amenable to treatment with hormone therapy. Vaginismus is more common in younger women and less important after menopause.

It is difficult to determine the true effect of HT on sexual function based on the literature published so far, partially because of the different drugs and doses that have been used in clinical trials, different tools to evaluate sexual function, and the differences in the particular populations studied.

Nevertheless, a Cochrane review published in 2013 assessed the effect of HT on sexual function in perimenopausal and postmenopausal women. It concluded that HT treatment with estrogens alone or in combination with progestogens was associated with a small to moderate improvement in sexual function, particularly pain, when used in women with menopausal symptoms or in early postmenopause (within five years of amenorrhoea), but not in unselected postmenopausal women. The levels of evidence were moderate to high.

The effects and benefits of HT included:
- Less pain
- Increased frequency of sexual activity
- Increased arousal
- Increased enjoyment of sex
- Increased number of orgasms
- No effect on libido, desire or interest in sex

**Hormone therapy (HT) for female sexual dysfunction**

**Hormonal treatment of Vulvovaginal atrophy (VVA)**

The aim of HT in women with VVA is to restore urogenital physiology and to alleviate symptoms. Non-hormonal approaches seldom restore premenopausal anatomy or physiology and do not provide a long-term solution. Systemic (oral or transdermal) HT effectively treats VVA in most cases, but will not be effective in 10-25% of women. However, it does also alleviate other menopausal symptoms, such as vasomotor symptoms, which in turn may improve both quality of life and sexual function as a whole.

Local vaginal estrogen specifically aims at treating dryness and discomfort during intercourse and is 100% effective in VVA. It will also reduce episodes of recurrent urinary tract infections (UTIs). It has no systemic effects. Consequently, progesterone is not needed to protect the endometrium, but there will also be no effect on other associated symptoms of menopause.
Androgens and the menopause

Androgens are produced by the adrenal cortex and the ovaries. Although the declining levels of estrogen are specifically related to menopause, it is important to remember that circulating blood levels of total and free testosterone, DHEA, DHEA sulphate (DHEAS) and androstenedione decline with age, commencing a lot earlier than the late reproductive years, and are not a consequence of menopause per se. There is no acute change in androgens across the natural menopause.4

Surgical menopause is associated with a significant reduction in testosterone, and lower androgen levels have also been reported in women with primary ovarian insufficiency/premature ovarian failure (POI).

For female patients in South Africa, it is not possible to make a laboratory diagnosis of low testosterone levels. The assays in laboratories have been designed for male subjects, whereas they are insufficient to detect the low levels present in women. Furthermore testosterone levels below which a woman can be described as being androgen-deficient and mandatory levels below which testosterone should be supplemented have not yet been defined.

Several randomised clinical trials have demonstrated efficacy of testosterone in doses appropriate for women for the treatment of low sexual desire/arousal disorder. Positive results have been shown among naturally and surgically-induced menopausal women and those using or not using HT. Exogenous testosterone improved commonly reported sexual problems, such as diminished sexual desire and arousal, pleasure, and overall satisfaction.

The APHRODITE study was a double-blind, placebo-controlled, 52-week trial in which 814 women with hypoactive sexual desire disorder were randomly assigned to receive a patch delivering 150 or 300 μg of testosterone per day or placebo.5 At 24 weeks, the increase in the 4-week frequency of satisfying sexual episodes was significantly greater in the group receiving 300 μg of testosterone per day than in the placebo group (an increase of 2.1 episodes vs. 0.7, \( P < 0.001 \)) but not in the group receiving 150 μg per day (1.2 episodes, \( P = 0.11 \)). As compared with placebo, both doses of testosterone were associated with significant increases in desire, arousal, orgasm, pleasure, reduced concerns, responsiveness and self-image.

The rate of androgenic adverse events, primarily unwanted hair growth, was higher in the group receiving 300 μg of testosterone per day than in the placebo group (30.0% vs. 23.1%), but the overall incidence of adverse events was similar in the testosterone and placebo groups.

Guidelines for androgen therapy in menopause

The North American Menopause Society (NAMS) recommends the following with regard to androgen therapy:2

1. A trial of testosterone therapy may be considered in carefully selected postmenopausal women with female sexual interest/arousal disorder and no other aetiology for their sexual problems. Women must be informed of potential adverse effects and unknown long-term risks.

2. Women using testosterone should be monitored for adverse effects, including facial hair, acne, voice changes, clitoromegaly, and adverse changes in lipids or liver function tests. Blood testosterone levels should be checked intermittently to ensure that levels remain in the normal range for reproductive-aged women.

3. Formulations of testosterone approved for the treatment of men increase the risk of excessive dosing when prescribed for women.

4. There is currently no role for the use of DHEA in the treatment of female sexual disorders.

The long-term effect of testosterone on the cardiovascular system and breast remain a concern. There is as yet no evidence for (or against) long-term safety and women must be informed of these potential side effects.

During testosterone supplementation, laboratory tests can be used to ensure that testosterone levels remain in the normal range for reproductive women and that testosterone is not being overdosed. Before beginning therapy, free androgen levels and sex hormone binding globulin (SHBG) should be measured.
Testosterone supplementation should not be administered if SHBG is high or low.

In South Africa there are no testosterone preparations approved by the Medicines Control Council (MCC) for women. Furthermore, the testosterone transdermal patch that has been shown to be beneficial in women has been withdrawn from the market internationally. The dose of testosterone appropriate for female patients is approximately one tenth that for males and using available testosterone preparations intended for men results in unpredictable testosterone levels and a considerable risk of overdose. In addition to androgenisation, the effect on arousal is lost at high doses and the prescriber must also consider the potential risk of medicolegal problems.

Compounded products are without justification and are not recommended. These preparations are not subject to regulatory control and their contents are uncertain.

Over-the-counter products claiming to supplement DHEA are unlikely to contain an active form and are likewise to be avoided.

**Tibolone**

Tibolone is a unique chemical compound that is metabolized to estrogenic, progestogenic and androgenic metabolites.

It has comparable efficacy to estrogen in alleviating vasomotor symptoms, and has an anabolic effect on bone. Conversely, it is neutral on the endometrium and does not cause breast tenderness.

The potential benefits of tibolone on sexual function have been demonstrated in a trial in which it was compared with transdermal estrogen/norethisterone acetate (NETA) (50 μg/140 μg) in naturally postmenopausal women with sexual dysfunction. Four hundred women with a mean age of 56 years were included. Both treatments resulted in improved overall sexual function, as determined by scores on the Female Sexual Function Index (FSFI), an increase in the frequency of sexual events, and reduction in sexuality-related personal distress. However, in the per protocol analysis at week 24, FSFI scores were statistically significantly higher in the tibolone group, which the authors attributed to the combined estrogenic and androgenic effects of tibolone in comparison with estrogen/NETA. The greatest benefits were in terms of arousal and desire, leading to better scores for the orgasm domain and total score (Figure 2).

In South Africa, tibolone is the first choice for women who need HT and where desire and arousal are the main problems in terms of sexual dysfunction. With tibolone, it is not necessary to follow up for hyperandrogenisation.

**New developments**

**Ospemifene**

Ospemifene is a selective estrogen receptor modulator (SERM) that has been approved in the USA for the treatment of VVA in postmenopausal women.

The recommended dose is 60 mg/day. It has an estrogen-like effect in the vagina (increases superficial cells, decreases parabasal cells and lowers vaginal pH). It results in a small, but statistically significant reduction in dyspareunia. The most
A common adverse effect of ospemifene is an increase in vasomotor symptoms, which has been reported to occur in 10% of treated women.\(^7\)

**Combination conjugated equine estrogen/bazedoxifene**

Also in the USA, a combination of the SERM bazedoxifene (BZA) with conjugated estrogen (CE) is approved for the treatment of vasomotor symptoms and prevention of osteoporosis in women with a uterus. Bazedoxifene provides endometrial protection, so a progestogen is not needed.\(^2\)

In the SMART 3 study, 664 healthy postmenopausal women aged 40-65 years were randomized to BZA 20 mg/CE 0.625 mg, BZA 20 mg/CE 0.45 mg, BZA 20 mg, or placebo once daily for 12 weeks.\(^8\) Changes in vaginal maturation, vaginal pH, and severity of the most bothersome symptom of VVA from baseline were assessed at screening and at weeks 4 and 12. Compared with placebo, BZA 20 mg/CE 0.625 or CE 0.45 mg significantly increased superficial cells and decreased parabasal cells. Vaginal pH and most bothersome symptom significantly improved with BZA 20 mg/CE 0.625 mg compared with placebo. Improvements in vaginal dryness were also observed with both BZA/CE doses. The incidence of treatment-related adverse events was similar across treatment groups.

In conclusion, menopause and its transition represents a significant risk factor for the development of sexual dysfunction, which impacts greatly on a patient’s quality of life. Thankfully, the development of effective treatments has led to greater recognition of, and solutions for, this problem.

In women with FSD, non-pharmacological approaches should be used first, focusing on lifestyle and psychosexual therapy, moisturizers and lubricants. If required, proven effective hormonal therapeutic options are available.

**References**