The specialist authority for menopause & post reproductive health

Urogenital atrophy

The British Menopause Society (BMS) is the specialist authority for menopause and post reproductive health in the UK. The BMS educates, informs and guides healthcare professionals, working in both primary and secondary care, on menopause and all aspects of post reproductive health.

BMS consensus statements, prepared by specialists from the BMS medical advisory council, address key disorders and controversial topics relating to menopause and post reproductive health. They reflect new studies together with recent medical and scientific information from articles in professional journals, plus informal consensus.

The consensus statements are evidence-based, comprehensively referenced and peer reviewed and they are regularly updated.

Summary

This guidance refers to urogenital atrophy, a chronic and progressive condition due to estrogen deficiency, most commonly associated with the menopause. There is a potential negative impact on all urogenital tissue quality including the vulva, vagina, bladder and urethra. Symptoms may not become apparent for several years after the menopause and therefore any association is lost, with women accepting symptoms as a normal part of the aging process. There may be reluctance to discuss symptoms with a clinician and this is likely to be linked with under diagnosis and under treatment[1]. Urogenital atrophy has been described as a silent epidemic with lack of awareness affecting an accurate diagnosis and access to treatment[2,3]. Whilst vaginal estrogen (also referred to as local estrogen) therapy is the best-known treatment, newer drugs and interventions are now available.

Introduction

Vasomotor symptoms start during the peri-menopause, a time of transition from reproductive to post reproductive life. Long-term estrogen deficiency can be associated with an increase in cardiovascular disease and osteoporosis. The effect of lack of estrogen on urogenital tissue quality is an intermediate effect, often taking three to five years to become apparent. Exact prevalence rates are unknown[4], but most women are likely to be affected by some degree of urogenital atrophy and the number of affected women will increase with time from menopause if untreated. Women using systemic HRT may still experience symptoms of urogenital atrophy and can use vaginally delivered estrogen in addition to systemic HRT.

Terminology

Changing terminology has failed to improve recognition and treatment of urogenital atrophy. Other commonly used terms include genitourinary syndrome of menopause and vulvovaginal atrophy. Urogenital atrophy is a term which accurately describes the condition and is the term preferred by the British Menopause Society.

Aetiology

In a healthy vagina, the superficial mucosal cells shed approximately every four hours, releasing large amounts of glycogen, which support lactobacilli (healthy vaginal bacteria). Estrogen deficiency causes the mucosa to become thin, with a significant reduction in superficial cells (less than 10%). Consequently, there is a reduction in glycogen and lactobacilli, allowing vaginal commensal organisms such as E. Coli to become more predominant, with a rise in the pH of vaginal secretions (>5) and an increased likelihood of vaginal discharge. Below the mucosa, the lamina propria consists of connective tissue arranged in papillae. Fibroblasts, which produce collagen are the predominant cell type in the connective tissue. Post menopause, these cells become dormant (fibrocytes), and the collagen fibres in the dermal layer hyalinize and fuse. Mucosal thinning and an alteration in connective tissue quality along with fragmentation of elastin fibres results in a reduction in vaginal elasticity, which is linked to pain with penetration.

Symptoms

The most common symptoms experienced include vaginal dryness, itching, burning and pain with sexual intercourse, all of which can impact on desire. Neuronal function is adversely influenced by a reduction in blood flow and this in association with a decrease in normal vaginal secretions can affect sensation and sexual pleasure. Consequent loss of sexual intimacy has a negative effect on the quality of life of women and their partners[5]. However, urogenital atrophy is not a condition which exclusively affects sexually active women; vulvovaginal discomfort and urinary symptoms can affect any woman who is estrogen deficient. It is important to ask about potential symptoms as this information may not be volunteered, with women mistakenly believing the symptoms experienced to be an inevitable consequence of aging. Urinary symptoms include frequency, nocturia, urgency and dysuria, which can lead to misdiagnosis of urinary tract infection, but some women develop culture positive urinary tract infection. Urinalysis is important and depending on the results, a midstream sample should be sent to microbiology for microscopy and culture. Overactive bladder may be misdiagnosed or may coexist in women with urogenital atrophy.

Signs

Examination is essential, both to confirm the diagnosis and to rule out other conditions including vulval dermatoses, Lichen Planus, Lichen Sclerosis et Atrophicus (LSA), pre-cancer and cancer. It is important to note that there may be minimal signs of disease despite marked symptoms[6].

The clinical signs to look for include changes in tissue colour ranging from pallor to inflammation. The vaginal mucosa becomes thinner and more prone to trauma. This can lead to bleeding when inserting a speculum (or during attempts at penetrative sex). There is loss of tissue elasticity, loss of vaginal rugae and shortening of the vagina and it may be very difficult to open the blades of the speculum. There may be a reduction in normal vaginal secretions, but in some women an increase in vaginal discharge can be observed due to an alteration in the vaginal microbiome as described above. The urethra can become more prominent and, in some women, prolapsed, facilitating ascending infection, leading to urinary tract infection. Narrow range pH paper is a very useful adjunct to assist diagnosis, with a pH of 5-7 supporting the diagnosis in association with symptoms and other clinical signs. The fat content of the labia majora reduces in some women and the labia minora can become resorbed or fused, which can lead to either loss of the clitoris from view or exposure due to a reduction in mobility of the clitoral hood.

Treatment

Diagnosis is key and this depends upon being aware of the condition and how common it is. Both estrogen and androgen deficiency play a part in the aetiology of urogenital atrophy and in women with no contraindication to hormone therapy, replacing the deficient hormone(s) is the logical approach. Treatment should be started early, as the time to respond to therapy will depend on the degree of atrophy at the time of presentation. It may take three to four months for an improvement to become apparent, and the most severely affected women may take longer to respond (vaginal estrogen is best provided indefinitely with annual review).

Lifestyle modifications

These include smoking cessation and regular sexual activity if possible. Smoking increases metabolism of estrogen and regular sexual activity improves the blood supply to the vaginal mucosa and causes mechanical stretching of the tissues, which helps maintain elasticity reducing progression of urogenital atrophy. A sedentary lifestyle has been observed to be associated with an increase in prevalence of urogenital atrophy.

Specialist pelvic floor physiotherapist

The assistance of a specialist pelvic floor physiotherapist to help with exercises to reduce vaginismus or hypertonicity associated with anticipated pain on penetration can be useful. Supported use of vaginal dilators, can also be helpful in some cases.

Non-hormonal lubricants and moisturisers

Vaginal lubricants and moisturisers, which are available with or without a prescription, can be used in conjunction with vaginal estrogen therapy. Lubricants, primarily used for short term relief of vaginal dryness, may be water, oil or silicone based and should be used at the time of sexual activity to reduce discomfort. It is important to remember that oil-based lubricants can weaken condoms in women dependent on

barrier contraception. It can be useful to combine water and oil-based lubricants, producing a 'double glide' effect. Moisturisers are recommended to be used at least twice weekly, irrespective of sexual activity. They affect the fluid content of the epithelium, replace normal vaginal secretions, which relieves dryness and the pH of the vaginal secretions is returned to normal (<5)[7]. To minimise any adverse effect on the vaginal microbiome, the pH and osmolality of recommended lubricants and moisturisers should be similar to that of naturally occurring vaginal secretions[8]. Lubricants and moisturisers are first line recommended treatment for women for whom estrogen is contraindicated. This group includes women all women diagnosed with breast cancer and particularly those who are taking aromatase inhibitors.

Vaginal estrogen

Guidance from the National Institute for Health and Care Excellence (NICE), published in November 2015[9], stated that vaginal (local) estrogen can be used for as long as needed. It also made clear that there is no need for endometrial surveillance or the addition of a progestogen for endometrial protection with the current low dose vaginal estrogen preparations in use. A Cochrane Database Review has drawn similar conclusions[10]. Vaginally delivered estrogen enhances blood flow which restores cell maturation, healthy bacterial flora and a pH below 5. Vaginal secretions and peripheral nerve function are improved with optimal symptom relief and low systemic absorption[11]. Vaginal estrogen therapy has also been found to be superior to placebo for urinary symptoms including urgency, urge incontinence, frequency and nocturia and should be considered in conjunction with anti-cholinergic drugs for women with symptoms of overactive bladder. Treatment choices include natural estrogens, such as estradiol (E2) delivered as a small vaginal tablet or ring or the weaker estrogen, estriol (E3) delivered as a cream (either 0.1% or 0.01%), a waxy pessary or an oily gel (see appendix – example pathway).

Absorption is greatest following initiation of treatment when the vaginal epithelium is most atrophic. Once the tissue quality has recovered, absorption of local estrogen decreases with minimal systemic effects and therefore smaller doses can be used to maintain the benefits achieved, hence a loading dose followed by a maintenance dose for most preparations[12].

It is important to inform women that although symptom control is usually seen within the first few weeks of treatment, a beneficial effect may take longer to become apparent, and treatment needs to be continued in order to achieve and maintain this. NICE recommends considering increasing the dose of vaginal estrogen in women failing to respond to treatment or with a history of breast cancer where symptoms are refractory to lubricants and moisturisers, after seeking advice from a healthcare professional with expertise in menopause/breast specialist. It is also important to ascertain the individual patient's preference as to the choice of product used or compliance will be poor. There would appear to be a low appreciation of available treatment choices and a lower uptake in the United Kingdom compared to Scandinavia and North America[13].

Vaginal dehydroepiandrosterone (DHEA):

The adrenal glands (80%) and ovaries (20%) secrete dehydroepiandrosterone (DHEA), a neurosteroid and precursor to sex steroid hormones and the exclusive source of estrogens and androgens post menopause[14]. Prasterone®, 6.5 mg a pessary containing DHEA delivered vaginally on a daily basis, is licensed in the UK to treat urogenital atrophy. When DHEA is delivered vaginally, it is converted into estrogens and androgens by enzymes within the epithelial cells of the vagina, but not the endometrium, as a result of a process known as intracrinology[15]. This results in maturation of the parabasal cells into superficial cells, with an associated increase in mucosal thickness and secretions. There is also an increase in collagen density in the lamina propria and stimulation of the muscle in the layer below, most likely due to the influence of the androgens, produced by DHEA, on fibroblasts. Ninety-five per cent of the active hormones made in the vaginal mucosa are inactivated at the site of synthesis preventing any increase in systemic hormone levels or a stimulatory effect on the endometrium. A phase 3 randomised placebo controlled, double blind, prospective study demonstrated a highly statistically significant beneficial effect in women with urogenital atrophy receiving DHEA in a dose of 6.5 mg, delivered daily vaginally for twelve weeks. Androgens can influence structural changes, due to loss of collagen and muscle, including a reduction in rugae and shortening of the vagina.[16] There are no topical androgen products available and use of vaginal DHEA is the only means of provision. Use of systemic hormone replacement therapy does not contraindicate use of DHEA delivered vaginally to treat urogenital atrophy. DHEA has not been studied in women with active or past breast cancer and use in women with a history of breast cancer is contraindicated, although use may be agreed following a discussion with the breast care team on an individual patient basis.

Ospemifene

Ospemifene is a selective estrogen receptor modulator (SERM), administered orally in a dose of 60mg once daily. It acts as an agonist in the vaginal mucosa, lowering vaginal pH and improving the Vaginal Maturation Index (VMI), and reduces symptoms including vaginal dryness and dyspareunia. There is an antagonist effect on the endometrium and breast tissue and it can be used in women with a history of breast and endometrial cancer, who have completed treatment but there is no clinical trial data for patients with current breast cancer. It is an appropriate choice for women who are not eligible for vaginal estrogen therapy or who prefer oral treatment to any form of vaginal treatment[17]. Hot flushes are the only consistent side effect associated with treatment with Ospemifene. Results associated with longer term use are not currently available and studies with extended follow up are required. This is particularly important as treatment for urogenital atrophy needs to be long-term.

Laser therapy

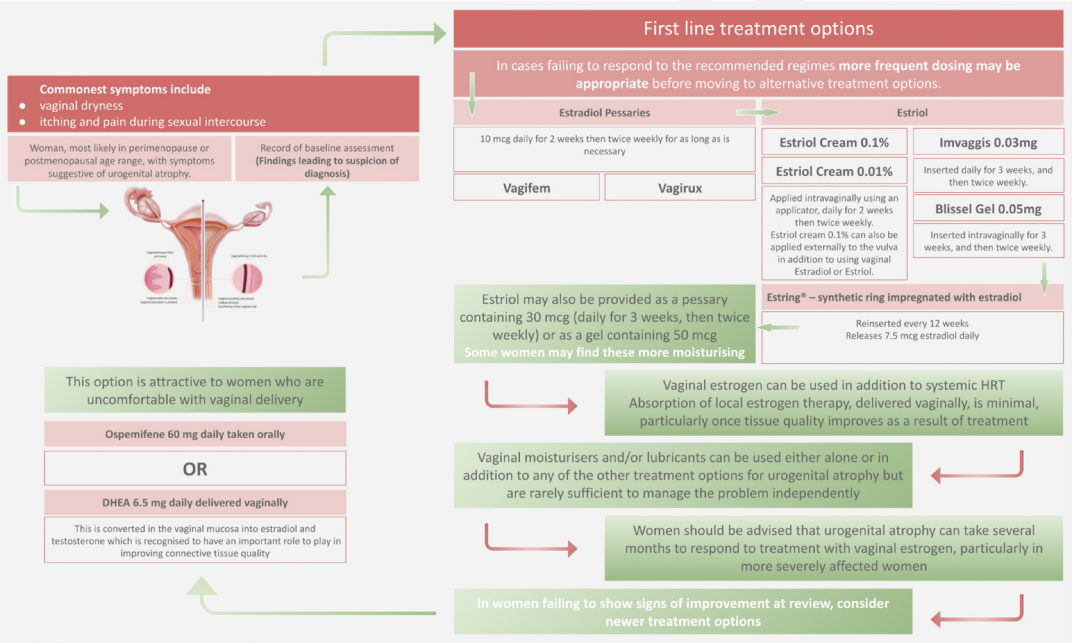
Laser therapy offers an alternative to the existing treatment choices already described and has the potential to provide benefits for women in whom use of hormonal therapy is contraindicated or who are struggling to adhere to existing treatment regimens for a variety of reasons including safety concerns, inconvenience, and sub-optimal response to treatment. This is a relatively recent development in available treatment options, thought to improve the blood supply to the vaginal epithelium, inducing collagen remodeling. It is based on the concept of water absorption, with

laser being attracted to any residual water within the connective tissue. The thermal effect produces oedema in the first few days following treatment and stimulates collagen producing fibroblasts, resulting in neocollagenesis and neovascularisation, using the body's own repair mechanism. This is associated with urogenital tissue restructuring, including an increase in collagen and sub-epithelial papillae and an increase in vaginal lubrication and acidity. The stratified squamous epithelium becomes thickened with an increase in glycogen and lactobacilli.

There are two types of laser therapy, CO_2 micro ablative laser (The MonaLisa Touch®) and Erbium Yag non-ablative photothermal laser therapy, (Juliet®). For both, treatment is delivered every four to six weeks, with three treatments initially, followed by a single annual treatment and although invasive, laser therapy offers choice, with treatment delivered much less frequently than with other options and independent of sexual intercourse. Although laser may be a valuable, non-hormonal method of treating urogenital atrophy, better quality evidence is required from randomized controlled trials.[18]

Appendix

Below is an example treatment pathway:



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