BMS | Consensus Statement

Urogenital atrophy

The British Menopause Society Council aims to aid health professionals in providing up to date and informed advice about post reproductive health. This guidance refers to the long term, but often ignored condition of urogenital atrophy resulting from postmenopausal estrogen deficiency.

Summary

Urogenital atrophy is more common than it would first appear and women do not always seek advice and guidance. Confusion still exists between systemic hormone replacement therapy (HRT) and local estrogen preparations but new treatment modalities have emerged that extend the range of options beyond lubricants, moisturisers and vaginal estrogen preparations.

Introduction

If vasomotor symptoms are considered as immediate consequences of the menopause, then symptoms related to urogenital atrophy would be considered intermediate, taking 3-5 years to become noticeable. Symptoms include: vaginal soreness, pruritus and dryness which can lead to dyspareunia and sexual dysfunction. It has been noted that women with positive scores for female sexual dysfunction (FSD) are 4 times more likely to have vulvovaginal atrophy than women who do not report symptoms (1). Vaginal dryness and dyspareunia also increase as estrogen levels decrease (2, 3). Women in their 70s now have a different, more liberated upbringing than the previous generation, who grew up in the post-war era, and so sexual function is more highly valued and expected in the 60s, 70s and beyond (4).

Atrophic changes to the trigone and urethra will cause symptoms of pseudo-cystitis, i.e. frequency, urgency and even dysuria, without positive mid-stream urine cultures but also will increase the incidence of genuine infection. Despite this, the incidence of atrophic change is difficult to estimate as many women accept the changes as inevitable and do not seek help. Over 30 years ago, a Swedish study reported 2 out of 3 women in their mid-70s had symptoms related to atrophy (5) and in a Dutch study of over 2000 women, 27% complained of vaginal dryness, soreness and dyspareunia with 36% reporting recurrent urinary tract infections and incontinence (6). It is also entirely possible to have the appearances of atrophy but to be minimally symptomatic (7).

Overall, approximately 60% of women who are post-menopausal and who have not had systemic HRT suffer from atrophic change and with the trend to prescribe low dose estrogen, up to 25% of women using systemic HRT will still experience symptoms of urogenital atrophy (8). There is a reluctance on the part of women to discuss intimate symptoms with their healthcare professionals (HCP) but the medical profession must also accept that very often they do not enquire about this set of symptoms as it may lead to further uncomfortable discussions regarding psycho-sexual difficulties (9). Also there is a confusion in the minds of both lay-public and doctors as to the difference between local and systemic estrogen and the lag phase of 3 to 5 years from the time of the menopause to the onset of symptoms means that the menopause is often not considered in the list of differentials when women do present. Finally, the changing nomenclature has also added to confusion, atrophic vaginitis, urogenital atrophy and now, genito-urinary syndrome of menopause (GSM) has been advocated by the North American Menopause Society (NAMS) (10), although many criticise this as labelling a natural change as a 'syndrome'.

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Patho-aetiology

There are estrogen receptors present in the squamous epithelium of the proximal and distal urethra, alpha receptors in the urethra sphincter, the trigone of the bladder (11), uterosacral ligaments, pelvic floor musculature (12) and vagina. Zhu has estimated 1-6% of estrogen receptors are present at various sites (13). This is entirely in keeping with the fact that the bladder and vagina were derived from the same embryological source – the urogenital sinus. This explains the prevalence of both vaginal and urinary symptoms associated with the condition, although the latter is very often overlooked. Estrogen deficiency can cause shortening and loss of elasticity of the vagina together with a reduction in secretions and thinning of the vagina epithelial layers (14, 15). The lack of lubrication enhances friction and with the thinning of the vaginal epithelial layers, increases the risk of micro-trauma resulting in infection. This risk is increased due to the glycogen depletion in the mucosal cells which produces a reduction in lactobacilli colonisation and therefore a rise in vaginal pH, reducing the natural acidity which normally forms a barrier to infection. Transudate caused by inflamed and thinned vaginal epithelium can be mistaken for infection and it is pertinent to perform a high vaginal swab, particularly as there may be an associated musty malodour which can be confused with genuine infection. Similarly, bladder pain, frequency and urgency can be mistaken for genuine urinary infection, which is statistically more common, but may represent pseudo-cystitis. A mid-stream urine sample should be taken to differentiate. Hypo-estrogenisation can cause reduced reduction in nerve transmission and alteration of proprioception such that previously erotically pleasant sensations can now be perceived as noxious; reduction in blood flow and lack of vaso-congestion further deteriorates the situation (16).

Treatment

The key is diagnosis which depends upon being aware of the condition, its prevalence and consequences. All postmenopausal women should be questioned about this regardless of their reason for presentation. It is also sensible to examine both for the presence of atrophic change, incontinence and prolapse in this age group. Principles of treatment of established urogenital atrophy are the alleviation of symptoms and the restoration of a more normal blood supply and epithelial mucosa. Treatment should be started early and the time to respond to therapy will depend on the degree of atrophy at the time of presentation. Most studies agree it takes 3 to 4 months to gain maximum improvement but some studies demonstrate as long as 6 months if the patients were severely atrophic initially. Short courses of treatment for only 3 to 4 months result in a recurrence of symptoms and many patients who are limited to just an annual short course resent the time they spend with resurgence of soreness and dryness. Different countries have different licensing regulations. In Scandinavia, local estrogen treatment can be prescribed indefinitely and in the United Kingdom, indefinitely with annual review.

Non-hormonal lubricants and moisturisers

Lubricants and moisturisers are both available without prescription although some can be prescribed. These are mainly a combination of protectants and thickening agents in a water-soluble base and are primarily used to relieve vaginal dryness during intercourse. They do not however provide a long term solution or restore normal physiology (17, 18). Some lubricants are available in both an oil-based and water soluble version and it can be useful to apply the latter on top of the former, a 'double glide' effect can be achieved as oil and water are immiscible. Some moisturisers are hydrophilic and therefore attract water and help retain fluid in the superficial cells of the vagina so that they have a longer effect. Vaginal lubricants and moisturisers can be used in conjunction with topical estrogens. A recent study has shown a distinction between some of the commercially available lubricants and moisturisers and it has been suggested that products that have optimally balanced osmolality and pH should be chosen as they are more physiologically similar to the natural vaginal secretions (19). Lubricants and moisturisers are particularly relevant in women with a genuine contraindication to estrogen, for example, breast cancer patients on aromatase inhibitors (AI).

The integrity and efficacy of condoms may be compromised by lubricants such as petroleum based products and baby oils. This is particularly important in the late peri-menopause when pregnancy is still possible and also to prevent sexually transmitted diseases (20).

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Estrogen

The publication of the NICE guidelines on Menopause diagnosis and management in November 2015 (21) acknowledged not all climacteric problems were centred on vasomotor symptoms and highlighted the issue of vaginal atrophy. It stated that local vaginal estrogen could be used for as long as it was needed whereas previously prescriptions were often issued for only 3 months at a time. The NICE guidelines also pointed out that there was no risk of hyperplasia and therefore no need for endometrial surveillance or additional progestogen for endometrial protection with the current topical estrogen preparations in use. Other papers, including a Cochrane Database Review, have drawn similar conclusions (9, 22, 23, 24). Conjugated Estrogen cream has now been removed from the market in the UK, as it was readily absorbed into the circulation and had been known to cause endometrial stimulation and bleeding (22). Absorption is greatest during the first few days of treatment when the vaginal epithelium is still atrophic, with increased vascularity and reduced thickness of the superficial layer. Once the epithelium has matured, the absorption of local estrogen decreases and therefore smaller doses of estrogen will prevent recurring atrophy hence a loading dose followed by a maintenance dose for most preparations.

Local therapy options include natural estrogens, such as estradiol tablet or ring, or the weaker estrogens, estriol, by cream. Such systemic absorption that does occur with estradiol vaginal tablets or ring, is very low and equal to or less than the postmenopausal adrenal gland output. There is more absorption associated with estriol as seen in creams (25), but as estriol is a weak estrogen which is not converted to estradiol, the systemic effects are limited.

Currently, phase 3 trials are ongoing with a novel estradiol muco-adhesive ovule/capsule where no applicator is required. It uses low and standard dosage and reports achieving 2 to 3 times less the systemic absorption of current preparations (26).

However, the presentation of unexpected postmenopausal bleeding should always be investigated.

All routes of estrogen administration are effective in the treatment of urogenital atrophy but low dose vaginal preparations are as effective as systemic estrogen therapy (27) so that if the presentation is one of local symptoms only then local treatment should be prescribed. Low dose vaginal preparations are effective for vaginal dryness, pruritus, dyspareunia (22, 27) and also reduced the risk of genuine urinary tract infections (28). Estrogen was also found to be superior to placebo for urge incontinence, urinary frequency, nocturia and urinary urgency. Estrogen significantly increased the first desire to void (FDV) to bladder emptying time and also increased bladder capacity (29). A small randomised trial has also shown that in cases of proven detrusor overactivity (DO), anti-cholinergics plus HRT are superior to anti-cholinergics alone, although, both are better than placebo (30). NICE guidelines have also suggested that if atrophic changes are present in a known case of overactive bladder (OAB) symptoms, topical estrogens should be prescribed in conjunction with anti-cholinergics (31). Topical estrogen does not have an effect on stress incontinence, although overall there appears to be a subjective improvement in urodynamic stress incontinence. There was no significant objective reduction in fluid loss although the maximum urethral closure pressure was increased significantly with estrogen therapy (32, 33). Some women will complain of a discharge related to the use of topical preparations although tablets and rings cause less discharge than creams which can be cumbersome and messy to insert and require the applicator to be dismantled, cleaned and reassembled. Clearly, discussion is required 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 treatments on offer and a lower uptake in the United Kingdom compared to Scandinavia and North America (34).

Atrophic changes at the cervix can render cervical smears unsatisfactory for assessment. In an age group where the screening programme is conducted at 5 yearly, rather than 3 yearly intervals it is extremely important that cervical cytology specimens are easy to read. Moreover, patients are unlikely to return if they are recalled with an unsatisfactory result if they found the examination painful. The squamo-columnar junction may recede into the cervical canal and the cervical os may tighten which also renders colposcopic assessment difficult. It is wise to consider the use of topical estrogen in women who are postmenopausal and are not on systemic HRT for at least 2 to 3 months prior to their cervical screening to facilitate the process.

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Women suffering from breast cancer that is estrogen receptor positive and those with gynaecological cancers that are hormone-sensitive pose a particular problem. Vaginal atrophy with its consequent soreness, pruritus and dyspareunia is an added burden for women already suffering from low self-esteem and change in body image and may in fact cause considerable pressure on a relationship at a time when emotional support is most required. Most oncologists are opposed to the use of even vaginal estrogen, in the presence of aromatase inhibitors but low dose topical estrogen in the presence of Tamoxifen, as anti-estrogen cover, is acceptable although discussion should take place with the surgical and oncology team. Occasionally, if symptoms are severe and the prognosis is not altered adversely, it may be appropriate to change the patient from an aromase inhibitor to Tamoxifen to allow treatment with topical estrogens. This would be the decision of the Oncologist. The grading and staging of the disease is also relevant and on humanitarian grounds, in late stage tumours, the quality of life is the most important consideration (35).

Ospemifene

Ospemifene is an orally active, selective estrogen receptor modulator (SERM) which has been licensed for use in the United States since 2013. The biological action is mediated through the binding of ospemifene and its major metabolite to estrogen receptors. It is currently indicated in Europe for the treatment of moderate to severe symptoms of vulva and vaginal atrophy in postmenopausal women who are not candidates for local vaginal estrogen therapy. Ospemifene may be used in women with breast cancer once treatment is completed although it has not been formally studied in women with a prior history of breast cancer. Short duration studies show efficacy regarding vaginal dryness, vaginal pH and sexual function (36, 37). To date there are 32 clinical trials involving 2,500 subjects but there is symptom data for only 12 weeks although we have 52 weeks of data for physiological changes and safety. There appears to be endometrial safety (36, 38) and minimal risk of venous thromboembolism (39). The main reasons for discontinuation were hot flushes (8.5%) and urinary tract infections (6.5%).

Laser therapy

Vaginal laser therapy is now being proposed as an outpatient medical treatment which is free from side effects and provides a marked improvement in sexual response. The theory is based on a thermo-ablative effect on the vaginal wall which triggers an improvement in collagen production within the vaginal submucosa. The laser energy is delivered to the vaginal tissue using a pixel pattern promoting faster healing and vaginal wall regeneration. There are protagonists for both the carbon dioxide laser (40) and the infra-red or Ebrium laser (41, 42). It has been suggested that results show an improvement in vaginal tightening, vaginal dryness and also stress incontinence and lichen sclerosis. Current studies have low numbers of women, a maximum of 12 to 18 months follow up. It is probable that 3-4 treatments would be needed, each lasting 30 minutes and some women need to repeat the treatment cycle after a year. Comments have also been made that women with good collagen respond more quickly (42) and that the laser works better with topical estrogen than on its own (40). Occasional adverse events have been reported including: burns, changes in menstrual cycle, vaginal discharge and in 11% involuntary urinary leakage. This could be a successful treatment that is in its early phase of evaluation.

Dehydroepiandrosterone (DHEA)

DHEA has no systemic absorption and is converted locally to estradiol and androgen and initial studies look promising. (43, 44). It is not yet available in the UK and we have no data to corroborate its safety in breast cancer patients, or if it would be as helpful as estradiol in cases of overactive bladder.

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Practice points

- Urogenital atrophy is common but usually under-recognised and under-reported and certainly in this country, the uptake of treatment is low.
- Women are sexually active longer now than in previous generations and are vocal in requesting a quality of life.
- Treatment should be continued to maintain benefits and once stopped, there will be a gradual resurgence of atrophic symptoms which may be purely vaginal, urinary or a combination.
- All local estrogen preparations are effective and therefore a patient's preference should be considered to maintain compliance.
- Progestogen is not indicated for endometrial protection and local estrogen treatment is regarded safe in terms of venous thromboembolism and cancer risk.
- Vaginal moisturisers and lubricants can be used in conjunction with topical estrogen or alone in cases where there is a medical contraindication to local treatment. Newer treatment modalities are becoming available but robust data is limited and evaluation is in its infancy.

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