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REVIEW

Vulvovaginal atrophy in women after cancer

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ABSTRACT

The number of women surviving longer after a cancer diagnosis is increasing. This means that more awareness regarding their health is required. This review will focus on vulvovaginal atrophy (VVA)/genitourinary syndrome of menopause, one of the most distressing adverse iatrogenic effects of the menopause, secondary to cancer therapies. The cancer therapies themselves, such as radiotherapy, chemotherapy, and surgery, have a direct impact on the lower genital tract which interplays with the ensuing hypoestrogenic state of the menopause. Symptoms of VVA are still under-reported and undertreated as neither clinicians nor patients are forthcoming in discussing the problem, despite its profound negative impact on quality of life. In terms of treatment of VVA, this review will look at the use of various options, including estrogen post cancer diagnosis, as well as considering newer emerging therapies such as dehydroepiandrosterone, ospemifene, and laser. The care of a woman post cancer diagnosis should be a multidisciplinary responsibility. However, further research is required into emerging treatment options as well as long-term safety data, to ensure all health-care providers and women are fully informed and confident to effectively address the impact of VVA post cancer diagnosis.

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Cancer in women

Cancer refers to a group of diseases characterized by abnormally dividing cells and is a leading cause of death. Worldwide, cancer was responsible for 9.6 million deaths in 2018 alone[1]. Breast cancer is the overall second most common cause of cancer in both men and women; however, it is the fifth most common cause of cancer death[1]. In the USA, there are currently 3 million women living with breast cancer, where the 10-year survival rate is 83%[2]. In the UK, breast cancer survival has doubled over the past 40 years. There were over 55,000 new cases of breast cancer in the UK in 2015 alone and 87% of these women will live with their diagnosis for 5 years or more, with 65% of women surviving for 20 years or more[3]. The improvement in survival rates in recent history means more women are living longer after their diagnosis and more awareness of their health needs is required. This review will focus on vulvovaginal atrophy (VVA) when it occurs as one of the adverse iatrogenic effects of the menopause secondary to cancer therapies (e.g. chemotherapy, radiotherapy, or removal of the reproductive organs). There will be an emphasis on VVA in women with breast cancer, as treatment often involves hormonal modulation.

Effects of cancer therapy on the genital tract

Radiotherapy

Ionizing radiation has a damaging effect on gonadal function. The degree of damage is dependent on the dose, the radiation field, and the age of the patient, with older women being at greatest risk due to reduced ovarian reserve. The pelvis and therefore the ovaries are exposed in the treatment of pelvic, abdominal, and lymph node cancer[4]. Radiotherapy used in central nervous system malignancies and cranial radiotherapy can lead to hypothalamic amenorrhea[4].

Pelvic radiation disease is an interplay of chronic symptoms which occur following radiotherapy to the pelvis, including effects to the urological, gastrointestinal, and bone systems, as well as sexual morbidity and early menopause[5]. Radiotherapy initially damages the mucosal lining of the organs in the field, which leads to inflammation and cell death. After radiotherapy is completed, tissue damage and scarring often ensue[5].

Chemotherapy

Amenorrhea is a well-recognized occurrence following chemotherapy and increases with age due to a reduction in ovarian follicles and cytotoxicity. Chemotherapy regimens, with repeated cycles, dose-intensive cycles, alkylating agents, and tamoxifen, are associated with higher rates of amenorrhea[6]. Amenorrhea is associated with longer disease-free survival and overall survival following chemotherapy in breast cancer patients, especially with estrogen-receptor-positive, early-stage cancer[7].

Graft-versus-host disease

Graft-versus-host disease is a complication of allogeneic peripheral blood stem cell transplantation and is a systemic

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T-cell-mediated immune response leading to inflamed and atrophic tissue[8]. Women with chronic graft-versus-host disease may have vaginal dryness, itching, burning, pain, dysuria, and dyspareunia, and the disease can even affect children. Moreover, genital involvement may be the only manifestation of graft-versus-host disease[9]. Anatomical distortion of external and internal genitalia has been reported, due to mucosal and sclerotic changes[9], and can present in various ways, including vaginal obstruction[8]. These problems are often compounded by the presence of VVA resulting from the hypoestrogenic state of iatrogenic menopause, which almost invariably follows total body irradiation and pre-stem cell transplantation.

Vulvovaginal atrophy/genitourinary syndrome of menopause

VVA occurs due to decreased estrogenization of the vaginal tissue and is therefore most common after the menopause. This can cause vaginal dryness, soreness, postmenopausal bleeding, and irritation, as well as urinary symptoms such as frequency, urgency, and urge incontinence[10]. The response of VVA to topical estrogens is rapid and sustained[11]. Unlike other symptoms and signs of the menopause, VVA is progressive over time. Symptoms are both variable and common, and include a decrease in vaginal rugae, decreased blood flow to the vaginal epithelium, an increase in vaginal pH, and a shift in the vaginal maturation index. The lower urinary tract has the same embryonic origin as the vagina and vulva, and decreased estrogen also leads to urinary symptoms such as dysuria, urgency, and recurrent urinary tract infections[11]. These symptoms are being increasingly recognized as part of the pathophysiology of VVA, and hence there has been a proposal by the International Society for the Study of Women's Sexual Health and the North American Menopause Society to use the term genitourinary syndrome of menopause which encompasses both VVA and urinary symptoms[12]. When this article refers to VVA, both vulvovaginal and urinary symptoms are implied.

It has been shown that severe VVA, particularly when confirmed by clinical examination, has an adverse impact on quality of life[13]. It also impacts interpersonal relationships, daily activities, and sexual function[11,14]. However, the true prevalence may never be known as it is often underreported, underinvestigated, and undertreated. This is especially true as there are varying cultural attitudes amongst women and health-care providers in discussing VVA[11]. It is clear that VVA-type symptoms post cancer result from a complex interplay due to the treatments used for the cancer itself as well as the ensuing menopausal status.

Patient's perspective

Over 50% of postmenopausal women, particularly those on aromatase inhibitors, experience VVA. A survey included consideration of the use of hormone therapy for the many effects of the menopause, not only VVA[15]. The findings suggested that younger patients were more concerned about recurrence of breast cancer with the use of hormone therapy. However, they were also more concerned about impairment of quality of life, and therefore were more likely to consider use of hormone therapy, although the actual percentage willing to use it was still quite low at 34%. This may be reflective of a generalized fear of hormone therapy following breast cancer diagnosis, not only in women but also in health-care providers. Limitations of these data were the age group studied and the small sample size. A larger study is needed in women who are postmenopausal following cancer treatment, assessing not only symptoms but quality of life related to VVA.

Various scoring systems have been devised to assess the severity and treatment response to VVA. The Day-to-Day Impact of Vaginal Aging (DIVA) score correlates well with women's self-scoring in activities of daily living, emotional well-being, body image, and sexual function; depression and urinary incontinence negatively impact on their self-scoring[16]. Other scoring systems for assessing quality of life are not specifically designed for assessing the impact of VVA; these include the Short Form-36[17] and the EQ-5D-3L[18] for patient self-rating in five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). The Female Sexual Function Index (FSFI)[19] has been validated in cancer survivors[20], but also does not directly address the symptoms and impact of VVA.

The Vulvovaginal Atrophy Questionnaire (VVAQ) is now being validated to advance knowledge and improve care of women with VVA/genitourinary syndrome of menopause. The VVAQ not only identifies women who would benefit from care, but also allows follow-up of the impact of treatment[21]. This is especially important as it has recently been found that women already on treatment report the worst symptoms[22]. This reflects that treatment has only been sought out once the VVA symptoms have become intolerable.

There remains a need for early detection through education of the public and health-care professionals. A systematic biopsychosocial and psychosexual methodology is also needed to assess the treatment response in women with VVA who have a cancer diagnosis. This is a particularly difficult time in their lives when they have to cope not only with the negative impact of cancer on their emotional well-being, but also with the added physical burden of VVA symptoms.

Oncologist's perspective

In a recent survey of medical oncologists, 60% of postmenopausal women and 39% of premenopausal women were reported to have experienced VVA[23]. Although it is known that VVA is often a consequence of cancer treatment, just under half of clinicians explained this to the patient. Moreover, only approximately 25% of doctors directly addressed the issue without prompting from the patient; most did not address the issue at all, with the main reason being lack of knowledge on the topic. With respect to treatment, 41% referred the patient to a gynecologist, whereas 35% prescribed the treatment themselves. This further

highlights the need for widespread education for all health-care providers on the symptoms, signs, and treatments of VVA to enhance confidence in managing this distressing condition promptly.

Menopause health-care provider's perspective

The International Menopause Society's position is that, in women who have had breast cancer, non-hormonal therapy should be used as the first line; however, if it is ineffective, topical estrogen may be used at a low dose and following appropriate patient counseling, especially in those taking tamoxifen or aromatase inhibitors[11]. Following gynecological cancer, topical estrogen may not necessarily be contraindicated, although its use may be off-label. Although there are no data demonstrating an increased risk of recurrence, the decision to start either local or systemic hormone therapy must be individualized following patient counseling and communication with the oncology team[11].

The National Institute for Health and Care Excellence (NICE) UK guidelines advise all health-care providers to give patients information on menopause and fertility issues when undergoing cancer treatment, and advise referral to an expert as well as provision of all treatment options[24].

There is considerably more advice on the management of women on systemic hormone therapy than there is about local hormone therapy following a diagnosis of breast cancer[25]. The British Menopause Society's consensus statement on management of estrogen deficiency symptoms in women treated for breast cancer advises that lifestyle modification or non-hormonal treatments should be first line. However, if these are ineffective then, following specialist advice, low-dose systemic hormone therapy or topical estrogens may be initiated[26]. Topical estrogen is not recommended in women on aromatase inhibitors. However, switching from an aromatase inhibitor to tamoxifen may improve symptoms; this possibility should be discussed with the oncologist. If this is ineffective, then topical estrogens can be considered[26]. The British Menopause Society also highlights the importance of referral for psychosexual counseling and support for body image concerns[26].

This consensus statement from the British Menopause Society is in agreement with the recommendation of the North American Menopause Society (NAMS), which recommends non-hormonal treatment as the first-line treatment for women with breast or endometrial cancer. However, this depends on patient preference and counseling on risks and liaison with the oncology team, especially as, in some cases, only a short course of low-dose estrogen is needed to allow intercourse to resume, whereby thereafter lifestyle modification and non-hormonal treatments can be tried for maintenance of functionality[27].

The recent Women Informed to Screen Depending on Measures of Risk (WISDOM) survey, which included American gynecologists and primary-care physicians, noted that 34% and 17%, respectively, felt comfortable to prescribe hormonal therapy for women with a history of breast cancer, whereas 39% of gynecologists and 61% of primary-care physicians did not[28].

The American Cancer Institute addresses the use of hormone therapy in patients with a past history of cancer and has explained to patients that the evidence is inconclusive with regards to recurrence risk[29]. However, the evidence available is related to recurrence following exposure to systemic hormone therapy, and the specific issue of VVA is not addressed.

The various non-hormonal and hormonal treatment options which are now available in some countries facilitate individualization of therapy – these will now be discussed.

Non-hormonal treatments

Moisturizers and lubricants

The hypoestrogenic state of menopause disrupts the vaginal microbiome by decreasing lactobacilli, leading to an increase in vaginal pH. Both lubricants and moisturizers can relieve discomfort in mild-to-moderate vaginal dryness, and are of use in women who have a genuine contraindication to estrogen-containing products and in those who do not wish to take hormone therapy. There are, however, many differences in the wide array of products available. Moisturizers rehydrate tissue and mimic vaginal secretions. Their effect lasts 2–3 days by changing the endothelial fluid content and decreasing the vaginal pH. Lubricants are either water-based, silicone-based, or oil-based and are used prior to intercourse. The World Health Organization recommends an osmolality of under 380 mOsm/kg to minimize the risk of epithelial damage, as greater osmolality is correlated with mucosal irritation and has been associated with cytotoxicity. It is also of note that parabens are a common preservative. Parabens are weakly estrogenic and it is possible that they may pose a carcinogenic risk themselves. Where a patient and their practitioner have chosen a moisturizer or lubricant to treat VVA based on a background of breast cancer, it is recommended that a paraben-free vaginal moisturizer with an acidic pH and osmolality less than 380 mOsm/kg is used. It is therefore important to be aware of the precise contents of each preparation recommended to patients and that there is informative labeling of these preparations[14].

A recent randomized controlled trial showed no significant difference in symptom reduction with vaginal estrogen compared to a vaginal moisturizer, although it could be argued that the dose of the ultra-low-dose estrogen preparation was inadequate in some women. In conclusion, vaginal moisturizers and lubricants are a good initial treatment option as long as care is taken to choose one with the correct properties and formulation[14,30].

Ospemifene

Ospemifene is a non-estrogen selective estrogen receptor modulator derived from toremifene. It is used as an oral therapy for those in whom local estrogens are not desired or contraindicated and has been approved for use in the

European Union once breast cancer treatment has been completed, including any adjuvant therapies[26,31]. Ospemifene has demonstrated an anti-tumor effect on breast cancer models as well as positively affecting bone turnover. A double-blind, randomized controlled trial showed increased maturation and decreased use of lubricant, with a negligible effect on the endometrium, although hot flushes were reported[31]. An indirect comparison[32] with 10 μg vaginal estrogen showed similar changes in VVA, with ospemifene hence appearing to be at least as effective with a similar safety profile. Larger studies and a direct comparison would be ideal, as well as long-term safety data in women with a history of breast cancer.

Laser

Microablative fractional CO_2 and erbium lasers have now been used extensively in managing symptoms of VVA. They work to improve the epithelial layer by improving blood flow to vaginal tissues and subsequent new collagen formation. This modifies the genitourinary architecture and restores mucosa to a healthier condition; changes can be seen within 1 h after application[33]. Most data thus far have been observational, but one randomized controlled trial showed that laser treatment was effective in ameliorating VVA symptoms, with improvements shown in both physical and quality-of-life scores[34]. Further randomized and long-term studies are needed to assess for long-term safety and also for a direct comparison to other treatment modalities, but these lasers may well provide an effective and safe non-hormonal option for women with a history of cancer[35]. Laser treatment has been under review by the US Food and Drug Administration as there have been some reports of burning, scarring, dyspareunia, and recurrent pain. Also, there is still no clear consensus on the optimum choice between the various energy devices[36]. However, with further work and long-term safety data, these tools may become routinely available in the public as well as the private health-care sectors.

Hormonal treatment

Vaginal estrogen

Vaginal estrogen therapy is preferable when systemic estrogen is not needed, such as in VVA, and is available in a range of forms such as pessaries, cream, or a ring. Some systemic absorption occurs unless the formulation prevents this; most absorption occurs at the beginning of treatment when the vulva is most atrophic and then decreases once the epithelium matures[11]. Estrogens may stimulate the endometrium in a dose-dependent manner and no safety data from randomized controlled trials are available beyond 1 year of use. However, their long-term use is not contraindicated so long as the patient is aware of the possible risks and reports any unscheduled bleeding[11]. It is likely that vaginal absorption varies between women, but there are no studies to recommend individualized 'evidence-based' policy. In women on tamoxifen, the efficacy of vaginal estrogen may be compromised due to blocking of the estrogen receptors. This is not the case with aromatase inhibitors, where the symptoms of VVA tend to be more severe. Concern exists that the efficacy of the aromatase inhibitors may be compromised by local estrogens used in this context; their use should therefore be discussed carefully with the patient and the oncology team[11].

Vaginal estrogen is preferred to systemic estrogen for VVA as it is often more effective with little systemic exposure. Unlike other menopausal symptoms, however, VVA symptoms do not diminish over time, and hence long-term treatment is needed as symptoms usually recur once treatment has been stopped.

Studies have shown that, for VVA, ultra-low-dose vaginal estrogen is as effective as systemic estrogen with significantly lower serum levels; however, the pharmacokinetics are hard to assess accurately in postmenopausal women unless very sensitive mass spectrometry methods are used[37]. This is particularly important to know in women on aromatase inhibitors following a diagnosis of breast cancer.

Estrogen post breast cancer

Local estrogen is usually not recommended as a first-line treatment for VVA but can be considered after non-hormonal treatments have been trialed and after careful counselling[11,26,27]. There is a lack of good-quality evidence in terms of the risk of breast cancer recurrence following local estrogen therapy; however, it has been shown that low doses of topical estrogen can be effective with no increase in serum levels[37]. A nested case–control study[38] showed local estrogen was not associated with recurrence in patients who took tamoxifen, and no patients who were on aromatase inhibitors experienced recurrence. A cohort study of just under 1500 patients[39] using topical estrogen with a history of breast cancer showed no increased risk of recurrence and no deaths were reported. The advantage of topical/local estrogen in the context of breast cancer is that progestogen is not required; progestogen could potentially increase risk, as seen with long-term systemic hormone therapy. Further work is needed in studying disease recurrence, symptom relief, and quality of life over a long period of time, especially with low-level topical estrogenic formulations.

Estrogen post endometrial cancer

Endometrial cancer is the sixth most common cancer in women, with a 5-year survival rate of 97% if the disease is confined to the uterus[40]. Most have early-stage disease and therefore have a good prognosis following hysterectomy and oophorectomy, and possibly radiotherapy, rendering patients menopausal if they are not so already. Some types of endometrial cancer may be stimulated by estrogen, so there is a theoretical risk of growth of residual cells with menopausal hormone therapy (MHT). No differences in recurrence have been demonstrated, but there are no good data on survival rates[40]. By extrapolation, it is likely that local estrogen is safe following hysterectomy for early-stage endometrial cancer;

however, there are insufficient high-quality data and further research is required on quality-of-life outcomes and doses/types of MHT. There is no evidence that adding progestogen to local estrogen in this context is protective against recurrence and it is therefore not indicated.

Estrogen post ovarian cancer

The treatment of ovarian cancer often involves removing all visible tumor in the pelvis alongside hysterectomy and bilateral salpingo-oophorectomy, resulting in surgical menopause if the patient is premenopausal. There is concern that MHT may stimulate angiogenesis and activation of residual cells following treatment of ovarian cancer. There is currently a Cochrane review underway assessing MHT following ovarian cancer[41] as previous studies[42,43] showed that MHT did not negatively impact disease-free survival and had either a neutral or positive impact on overall survival. Extrapolation of these data infers that local estrogen therapy is likely to be safe in these women; however, further research is needed.

Testosterone

Vaginal testosterone is a potential treatment, and a systematic review showed that vaginal testosterone may lower the vaginal pH, increase the number of lactobacilli, and improve vaginal epithelial maturation[44]. A double-blind, randomized, placebo-controlled trial in women on aromatase inhibitors[45] showed improved sexual satisfaction, reduced dyspareunia, and reduced vaginal dryness, with no change in serum sex steroid hormone levels; however, this trial involved a small number of women exposed for a short period of time, and hence longer-term data and safety profiles are needed. One concern is that testosterone aromatized to estrogen in women not on aromatase inhibitors might be a risk for women with estrogen-receptor-positive cancer.

Dehydroepiandrosterone

Dehydroepiandrosterone is an inactive precursor for intracellular formation of androgens and estrogens, both premenopausally and postmenopausally. It is therefore a potential vaginal therapy for the symptoms of VVA. There have been a number of randomized controlled trials of dehydroepiandrosterone for VVA[46] which showed a rapid correction of symptoms and signs with 6.5 mg of prasterone inserted vaginally daily, as well as improving sexual health. However, women with hormone-sensitive cancers were excluded and further studies on long-term safety data are needed in women with cancer. This may be an option after individualized discussion and consent; at present, the European Medicines Agency has contraindicated the use of this product in women with breast cancer but the US Food and Drug Administration has only advised caution.

Dehydroepiandrosterone has been shown to be at least as effective as vaginal estrogens in treating sexual dysfunction in perimenopausal and postmenopausal women[47], and has been approved by the US Food and Drug Administration and the European Medicines Agency as a treatment for dyspareunia, but it has not yet been assessed in breast cancer survivors[48]. Further assessment and long-term data in breast cancer survivors are needed as it may be a good alternative option, especially as studies have shown that, over a 12-week period of daily administration, systemic estradiol levels remained within the expected postmenopausal range[49].

Multidisciplinary approach to managing VVA after cancer

The physical and emotional well-being of a woman after a cancer diagnosis is a multidisciplinary responsibility and all members of the health-care team should feel comfortable discussing VVA symptoms openly with the patient, especially as she may not be forthcoming with her issues. When deciding on and prescribing treatment, one should treat the woman holistically, considering her quality of life, informed consent, and transparent patient education. More research is needed as there is a paucity of good-quality long-term safety data on the various treatment options for VVA in cancer patients, as well as the physical and emotional impact that VVA post cancer diagnosis has on this subset of women who are increasing in number due to increasingly long survival rates. Allied health professionals such as oncologists, oncology nurse specialists, general practitioners, and general gynecologists require greater education on managing VVA, as these professionals represent the first port of call for many women wishing to seek help for their symptoms. Ideally, VVA should be discussed at initial cancer diagnosis so that timely referral to a menopause clinic can take place.

Conclusions

VVA is under-reported and undertreated, and this can lead to decreased quality of life in women. Due to a delay in seeking help, a lack of education on the matter, and a lack of data on the subject, the true prevalence and impact of VVA on women with a cancer diagnosis are unknown but certainly underestimated, and the condition is largely undertreated. There are now various treatment options available, a number of which need validation, longer-term safety data, and direct comparison with vaginal estrogens. More focused research is needed in this growing population of women and all disciplines need to be more vocal in addressing the issue. Both clinicians and women need to feel sufficiently empowered confidently to address and treat this distressing condition.

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