The Recognition and Management of Atrophic Vaginitis

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Abstract

The population of postmenopausal women in Canada is growing rapidly. It is now estimated that there are more than four million women in Canada over the age of 50. Menopause, hormone replacement and the sequelae of estrogen deprivation will become important foci for health care in this century.

Urogenital aging occurs as a result of estrogen deprivation in menopause and of tissue aging itself. Problems originate from the lower urinary tract (urethra and bladder) and from the vagina. Vaginal complaints include dryness, dyspareunia, discharge and/or bleeding. Estimates of prevalence suggest that 40–50% of postmenopausal women are affected. These symptoms, while not life-threatening, can be extremely uncomfortable and limiting, and can negatively impact on quality of life.

Estrogen replacement therapy has long been the mainstay of treatment for vaginal atrophy. Both oral and vaginal estrogen are effective, though the vaginal route is often chosen because it avoids the enterohepatic circulation and can therefore be given in much lower doses. Estrogen can be administered vaginally as a cream. Newer methods of delivery include estradiol vaginal tablets and sustained release intravaginal estradiol rings. Effective nonhormonal alternatives include the vaginal moisturizer, polycarbophil.

Many treatment options for vaginal atrophy due to estrogen deficiency now exist, and treatment can be customized to meet individual patient needs.

Introduction

Canadian women are living longer, with ever increasing numbers surviving well into their eighth decade. With the expectation of women living 30 or more years beyond menopause (one-third of their lives), issues that influence the quality of postmenopausal life should receive more attention now. Unfortunately, little attention has been directed to common postmenopausal concerns, including urogenital aging, a progressive and variable condition that occurs as a consequence of both estrogen deprivation and tissue aging.

The female introitus, vagina, bladder and urethra are all derived from the primitive urogenital sinus, and estrogen receptors have been identified in all of these structures,[1] as well as in the pelvic floor musculature and endopelvic fascia.[2] The vagina and the urethra, in particular, contain large numbers of high affinity estrogen receptors. The shared embryology of these organs accounts for their similar hormonal responsiveness, including the shared marked susceptibility to estrogen deprivation.

Symptoms of urogenital aging can be divided into two broad groups: those originating from the urethra and bladder (i.e., the lower urinary tract), and those originating from the vagina and vulva. This article will discuss the latter (i.e., vaginal atrophy), with particular attention given to therapeutic options currently available.

Epidemiology

Without estrogen replacement, urogenital aging would be an almost universal phenomenon in postmenopausal women. Not all women will be symptomatic, and of those who experience troublesome symptoms, only a minority will consider their complaints to be chronic and severe. The onset of symptoms is often insidious and can occur long after other menopausal symptoms, like hot flushes, have been resolved. Symptoms and signs of urogenital aging are highly variable in an individual as well as among individuals. Smokers may be at higher risk.[3]

The true extent of the problem is difficult to assess. Studies of the prevalence of urogenital symptoms in postmenopausal women are limited. Questionnaire surveys provide estimates that are generally higher than clinical experience suggests, because many women admit problems only in the anonymous format of a questionnaire. Failure to question patients directly also contributes to the lack of recognition. Health care providers may assume that patients receiving systemic hormone replacement therapy do not have urogenital atrophy and neither question nor examine for it. However, it has been estimated that approximately 40% of patients taking oral hormone replacement have persistent vaginal dryness.[4] Signs of atrophic vaginitis can be very easily missed during a routine vaginal examination, particularly if one is not looking specifically for it.

Stenberg *et al.* noted complaints of vaginal dryness in 43% of a large cohort of postmenopausal women aged 61 years, with dyspareunia in 41%.[5] Of this group, 15% cited additional symptoms, including vaginal itching, discharge and pain, while 32% had lost interest in sexual relations. Similar prevalence figures were reported in a recent American Gallup poll, where 55% of respondents admitted to vaginal dryness and 32% complained of dyspareunia.[6] Van Geelen *et al.* found an overall 27% prevalence of vaginal dryness and / or dyspareunia among non-institutionalized Dutch women aged 50–75 years.[7] In their survey population, almost half of the respondents noted moderate to severe discomfort, yet only one-third of this subgroup had sought medical care for their symptoms (Table 1).

It is estimated that there are now more than four million women in Canada over the age of 50 years. Applying the above estimates of prevalence would mean that, in the next decade, between one-and-a-half to two million Canadian

Table 1
Prevalence of Vaginal Dryness

Study	Prevalence
Stenberg *et al.*, 1996[5]	43%
Utian *et al.*, 1994[6]	55%
Van Geelen *et al.*, 2000[7]	27%
Iosif and Bekassy 1984[31]	38%

women will suffer from problems relating to vaginal atrophy—a staggering estimate. Vaginal atrophy is not a trivial problem.

Pathophysiology

After the menopause, circulating estrogen levels are low. Tissue aging also inevitably occurs. The vaginal epithelium becomes less cellular and thinner, with a gradual loss of rugal folds and an obliteration of the vaginal fornices. Elastic fibres fragment and lose integrity. Smooth muscle and collagen fibres in the vaginal walls similarly degenerate and undergo hyalinization. The vagina loses elasticity, shortens, narrows and becomes less distensible and more susceptible to trauma. Vaginal blood flow decreases,[8] as does secretion of vaginal fluid during sexual stimulation and coitus. With cellular thinning there is a loss of glycogen, decreasing the colonization of lactobacilli and lactic acid production. The usual acidity of the vagina, which serves as a potent defense mechanism, is lost. This leads to an overgrowth of enteric organisms in the vaginal flora, and an increased susceptibility to vulvovaginal infection.

Clinical Features

Symptoms

Common vaginal symptoms of urogenital aging include vaginal dryness, dyspareunia, itching, burning and discharge as a result of nonspecific inflammation or infection. Vaginal bleeding from trauma or coitus can occur.

Physical Findings

In the atrophic state, the introitus is relatively narrowed, and vaginal capacity is reduced. Speculum insertion can be more difficult. The vaginal mucosa appears pale and dry. The walls are smooth due to a loss of rugae. Epithelial tissues are often friable, and submucosal petechiae or even overt bleeding may be seen.

The diagnosis of vaginal atrophy is most often made by gross visual inspection of the vagina using a speculum. The addition of a vaginal pH measurement can improve diagnostic accuracy, with vaginal pH expected to be greater than 5.0.[9] Atrophic change in the vaginal epithelium can also be assessed cytologically via a smear taken from the lateral vaginal wall. The result is reported as a Maturation Index. Although this technique provides a means of objective assessment of the vagina, it is not often used clinically.

Treatment

Patient acceptability and preference must be considered important variables for the treatment of vaginal atrophy, since urogenital symptoms, in contrast to vasomotor symptoms, continue throughout life and require long-term treatment. Therapy should be easy to use and convenient, since long-term patient compliance is essential.

Although age-related changes cannot be reversed, most aspects of estrogen deficiency are reversed easily and rapidly. Estrogen, either local or systemic, has long been the mainstay of treatment for atrophic vaginitis. A large body of evidence now exists to show that vaginal symptoms readily respond to estrogen therapy.

While oral estrogen is effective for the treatment of urogenital atrophy, vaginal administration is often chosen because it avoids the enterohepatic circulation, and can be given in doses much lower than those required for the alleviation of hot flushes or the management of osteoporosis. Systemic estrogen replacement has side effects including vaginal bleeding and mastalgia, which may be unacceptable, particularly in the elderly patient. Systemic hormone replacement does not provide relief from symptoms of urogenital atrophy in some patients, so local therapy is needed as well. Raloxifene, an alternative treatment for postmenopausal osteoporosis, exerts an anti-estrogenic effect on urogenital tissues; its use may necessitate additional local estrogen administration.

Estrogen can be administered vaginally as a cream, a tablet or in a sustained-release intravaginal ring. All provide good clinical effect.

Conjugated Equine Estrogen Vaginal Cream

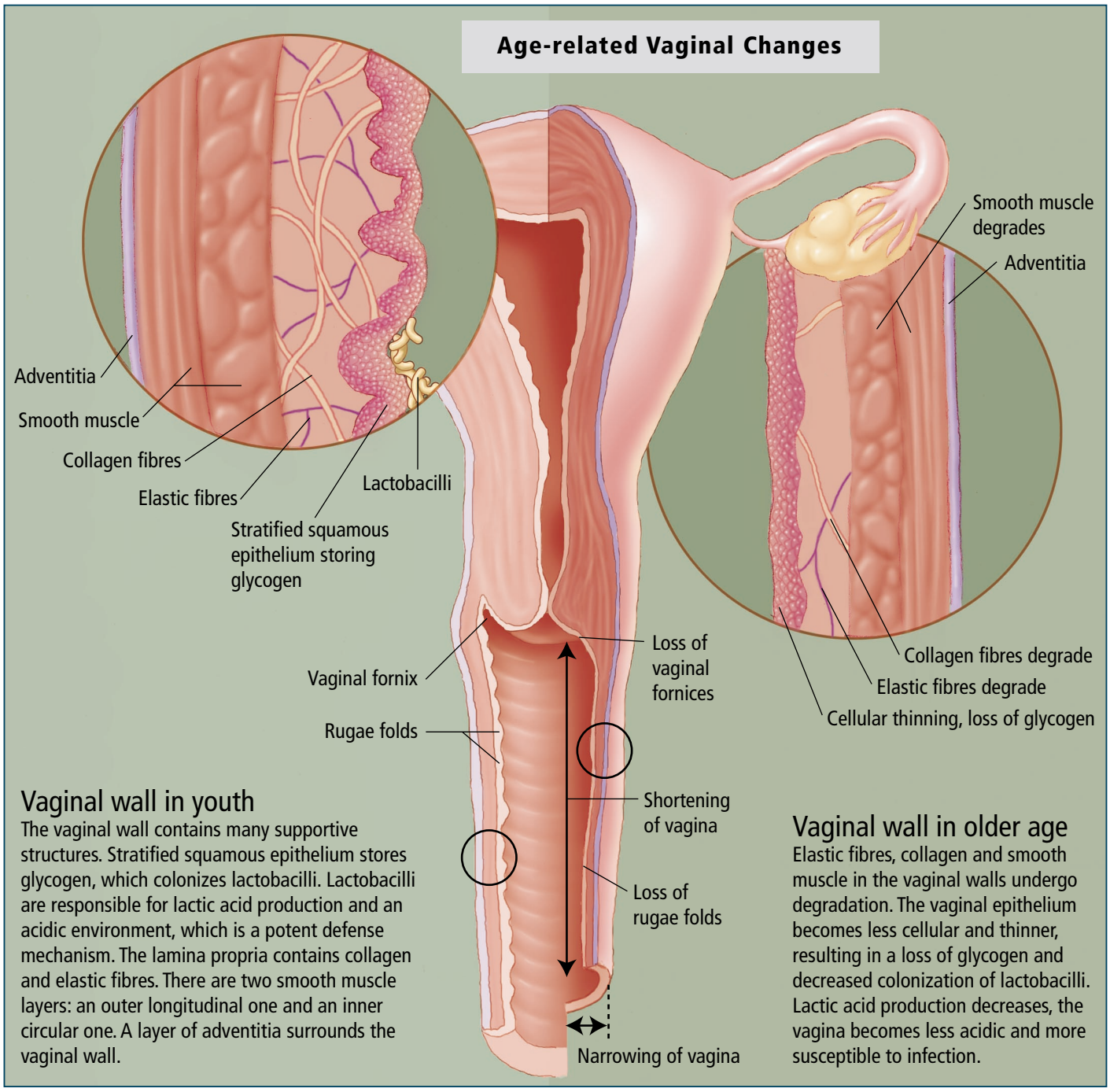
Estrogens are commonly given in the vagina in the form of conjugated equine

Table 2
Intravaginal Estrogen Preparations for Vaginal Atrophy

Preparation (generic)	Trade Name	Dose	Endometrial Proliferation	Availability in Canada
Conjugated equine estrogen cream	Premarin cream	0.3mg daily x 2 weeks, then 0.3mg twice weekly	Yes	Yes
Estradiol ring (sustained release)	Estring	One ring (2mg) q3months	No	Yes
Estradiol tablet	Vagifem	25µg daily x 2 weeks, then 25µg twice weekly	No	Yes

estrogen (CEE) cream (Premarin™ cream). Each gram of cream contains 0.625mg of conjugated estrogens. Daily administration of 0.3mg (one-eighth of an applicator) for two weeks and twice weekly thereafter for six months has been shown to correct vaginal atrophy both symptomatically and cytologically,[10] though other dosing schemes have been used with success (Table 2). To achieve similar effects on the vaginal epithelium, oral CEE is needed in much higher doses,[11] suggesting a superior efficacy of the local route.

Marked systemic absorption of estrogen (with a fall in FSH and LH levels) can occur from the vaginal cream, especially at the beginning of treatment when the vaginal epithelium is thin.[12] Endometrial proliferation from unopposed estrogen is a concern. In the above-referenced study by Handa *et al.*, 20 patients with documented atrophic endometrium were treated with 0.3mg vaginal CEE cream daily for six months. One patient did develop endometrial hyperplasia. However, Botsis *et al.* documented an absence of endometrial proliferation by ultrasound in women using similar doses of CEE cream for six months.[13] Therefore, it remains controversial as to whether or not management strategies for women using vaginal CEE should include annual endometrial surveillance by ultrasound or endometrial biopsy, or concomitant use of a low-dose progestin.



Vaginal creams containing estradiol and estriol have also been used successfully to treat vaginal atrophy. As with the conjugated estrogen cream, systemic absorption can occur.[14,15] Iosif reported proliferative change in the endometrium in seven of 48 patients receiving vaginal estriol suppositories for eight or more years.[16]

Intravaginal Estradiol Ring

Low-dose estradiol can be delivered via a flexible silicone ring with an estradiol-loaded core (Estring) inserted in the upper vagina. Hormone is slowly released in constant and extremely low doses (5–10µg / day) over a three-month period. Smith *et al.* demonstrated that the symptoms and signs of atrophic vaginitis improved, with restoration of normal vaginal pH and cytology in more than 90% of their patients using an intravaginal estradiol ring.[17] Serum estradiol levels do not rise to significant levels with the ring, with several authors noting a lack of endometrial proliferation,[18] even after one year of use.[19]

Advantages of the ring include not only the ability of the product to deliver uniform, sustained and local release of low doses of estradiol (as compared to those with intermittent local CEE cream), but also ease of insertion and improved patient compliance. Nachtigall found the estradiol ring to be an equally effective but more acceptable form for treatment of urogenital estrogen deficiency when compared to CEE vaginal cream.[20] Other investigators have reported similar findings.[21,22] However, patients with limited vaginal capacity or limited manual dexterity may not be able to insert and remove the ring easily, and those with pelvic organ prolapse may experience difficulty maintaining the position of the ring. Thus, the product is not ideal for all users.

Intravaginal Estradiol Tablet

Low doses of 17β-estradiol can be administered in the vagina using a hydrophilic slow-release tablet containing 25µg 17β-estradiol (Vagifem). Maintenance therapy involves the administration of one tablet into the upper vagina every three days via a preloaded single-use applicator. Upon contact with the vaginal mucosa, a gel layer forms, allowing for rapid diffusion of estradiol.

Eriksen and Rasmussen reported significant benefit over placebo with the vaginal tablet administered twice weekly.[23] After 12 weeks of treatment, 89% of patients demonstrated reversal of atrophic changes in the vagina and reported relief from vaginal dryness. Patient acceptability of the tablet was high. Similarly, a recent multicentre, open, randomized Canadian trial by Rioux and colleagues reported equal therapeutic efficacy with 17β-estradiol tablets and CEE cream for the treatment of vaginal atrophy.[24] The authors identified a lack of significant systemic absorption of hormone or endometrial effect with the intravaginal estradiol tablet. Other studies have reported similar findings.[25,26]

As with the estradiol ring, the major advantages of the estradiol tablet are its ease of use and high long-term patient compliance. In the study by Rioux *et al.*, a significantly higher number of patients reported the tablet as acceptable when compared to the cream. At study completion, 90% of tablet users continued with the treatment, whereas only 68% continued using CEE cream.

Nonhormonal Treatment Options

Unfortunately, not all women suffering with symptoms of vaginal atrophy can or will use estrogen therapy. Several alternative therapies have been proposed, although at the present time, there are few data regarding their effectiveness. The polycarbophil moisturizing vaginal gel (Replens), used three times a week, has been shown to be as effective as dienestrol cream for symptoms of vaginal atrophy in postmenopausal women.[27] This gel is a hydrophilic polymer that binds to vaginal epithelial cells and maintains hydration. Vaginal fluid volume, moisture,

elasticity and pH are improved, though cytologic change in the vaginal mucosa is not seen.[28]

Temporary relief from vaginal dryness and dyspareunia can be achieved using water-based lubricants (e.g., KY Jelly™) or even vegetable oil. Vaginal douching has not been shown to be helpful.

Lifestyle factors may also be important. Retrospective data suggest that continued sexual activity (vaginal coitus) may prevent the development of vaginal atrophy, presumably by maintaining epithelial blood flow and pH in the normal range.[29] Upmalis *et al.* identified no improvement in vaginal cytology as compared to placebo after 12 weeks of treatment with soy isoflavone extract tablets in 177 postmenopausal women.[30] Preliminary work has suggested that cigarette smoking may also have an adverse effect on the vaginal epithelium, increasing atrophic changes.

Conclusion

The menopause represents a unique challenge for health care providers. As more women enter their postmenopausal years, individual patient needs will differ and customized treatment options will be necessary. Symptoms of vaginal atrophy are common, and perhaps much more prevalent than is currently thought. Menopausal women need encouragement to seek help for these symptoms and health care providers need to be aware not only of the problem, but also of the variety of treatment options available for these symptoms, and the advantages and disadvantages of each. Simple approaches such as local estrogen replacement can provide great benefit for symptoms of vaginal atrophy in the menopause and significantly improve quality of life. ◆

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