VAGINAL ATROPHY: REVIEWING THE BASICS

Vagina
The vagina is a canal about 3 to 5 inches long. The vagina is composed of an inner stratified squamous epithelium, a middle muscular layer, and an outer fibrous layer. Mucus secreted by this lining keeps the inner surface of the vagina smooth and moist.

As illustrated in *Figure 1*, the normal vagina has several supportive structure elastic fibres, smooth muscles and a mucous membrane that stores glycogen which allows for lactobacilli to thrive. In premenopausal women, the acidic pH of the vaginal fluid is an important component of the nonspecific host defense against pathogens. With estrogen stimulation, the vaginal epithelium produces glycogen, which is broken down to glucose. Lactobacillus species metabolize glucose and produce lactic acid, which is responsible for the acid pH of the vagina.

*Figure 1*: The vaginal environment in its normal state vs. in the presence of vaginal atrophy (i.e. atrophic vaginitis)
Before menopause, in the presence of endogenous estrogen levels, the vagina is characterized by a thickened rugated vaginal surface, increased vaginal blood flow, and vaginal lubrication. Prior to menopause the vaginal epithelium is made up largely of intermediate and superficial cells with few parabasal cells.

The vagina maintains a delicate balance of bacteria and vaginal secretions; the resulting slightly acidic environment (pH usually between 3.5 to 4.5) helps maintain vaginal health. The bacteria that are present under normal conditions are referred to as normal vaginal flora. Any change in the vaginal environment can cause bacterial infection by altering the vaginal flora. Estrogen deficiency and treatment with antibiotics can make the vaginal secretions more alkaline. This, in turn, makes the vagina more susceptible to infection.

**Mini Quiz:**

1) **What prevents the growth of pathogen in the vagina?**

2) **What causes the pH of the vagina to be acidic?**

3) **What cell type(s) predominate(s) in the vagina before menopause?**

**Urogenital Atrophy**

Urogenital aging is, in part, related to estrogen deficiency. Significant physiologic changes occur during menopause due to estrogen loss. Proper maintenance of various tissues throughout the body requires estrogen. Without estrogen stimulation, these estrogen-dependent tissues atrophy and become more susceptible to damage. In the urogenital system, some of the most common symptoms are triggered by degenerative changes in the vulva, vagina, urethra, and bladder. *Table 1* lists the symptoms associated with urogenital aging.

**Table 1: Symptoms of urogenital aging**

<table>
<thead>
<tr>
<th>Vagina</th>
<th>Urinary</th>
<th>Prolapse*</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Dryness</td>
<td>• Recurrent urinary tract infection</td>
<td>• Incomplete emptying or voiding</td>
</tr>
<tr>
<td>• Irritation</td>
<td>• Frequent urination</td>
<td>• Introital bulge</td>
</tr>
<tr>
<td>• Itching (pruritis)</td>
<td>• Hematuria (blood in the urine)</td>
<td>• Constipation</td>
</tr>
<tr>
<td>• Dyspareunia (pain with intercourse)</td>
<td>• Dysuria (difficult or painful urination)</td>
<td>• Pelvic heaviness</td>
</tr>
<tr>
<td>• Post-coital bleeding</td>
<td>• Urgency</td>
<td>*Prolapse is the falling down or slipping of a body part from its usual position or relations</td>
</tr>
<tr>
<td>• Vaginal discharge</td>
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</table>

**Vaginal Changes**

The vaginal surface becomes thinner, less elastic, and more friable. Fewer secretions are produced, and production is delayed longer during sexual stimulation. As illustrated in *Figure 1* in the presence of vaginal atrophy (atrophic vaginitis) the vagina is shorter, loses the rugae and becomes less acidic through
the loss of the lactic acid producing lactobacilli. The vaginal walls may exhibit small petechiae (ie, pinpoint, nonraised, round, purple-red spots caused by submucous hemorrhage) and become thinner (often only a few cell layers thick), less elastic, and progressively smoother as folds decrease. Vaginal blood flow diminishes. Although the sebaceous glands remain prominent, their secretions diminish and the onset of lubrication during sexual stimulation is delayed.

Cytologic changes occur in vaginal epithelial cell types with an increase in parabasal and intermediate cells and a substantial decrease in superficial cells. In premenopausal women, intermediate and superficial cells predominate; few parabasal cells are noted.

The decrease in estrogenic stimulation which occurs after menopause causes a decrease in lactobacilli, which then shifts the vaginal pH toward alkalinity. The pH increases to 5.0 or greater from the premenopausal range of 3.5 to 4.5. This higher pH allows colonization of the vagina by fecal flora and other pathogens.

**Symptoms of Vaginal Atrophy**

Vaginal symptoms, which include vaginal dryness, vulvovaginal irritation and itching, and dyspareunia, are usually progressive and unlikely to resolve spontaneously. Left untreated, vaginal atrophy can result in years of vulvovaginal discomfort, with a significant impact on quality of life.

A population-based study of 438 women aged 45 to 55 years, found that the percentage of women reporting vaginal dryness increased progressively as women approached and go through menopause: from 3% in premenopause to 25% by 1 year and 47% by 3 years after menopause. Women who smoke, as well as those with diabetes, are more likely to develop symptoms of vaginal atrophy.

Recurrent urinary tract and vaginal infections are more likely in estrogen-deficient women. Whereas both systemic and local estrogen therapy will correct vaginal health, only local therapy reduces the frequency of recurrent urinary tract infection.

**A Significantly Underdiagnosed & Undertreated Condition**

It is estimated that 1 in 2 women are affected by vaginal atrophy within three years of menopause, however, only 25% will seek help. In the Canadian VIVA (Vaginal Health: Insights, Views & Attitudes) survey, 56% of women reported having vaginal atrophy symptoms for more than 3 years.

Many healthcare providers do not proactively raise this issue; in the VIVA survey, 59% of women reported that their healthcare provider had never discussed vaginal health. By the time women bring it up with their healthcare provider, most will have tried self-treating with over-the-counter products; 58% of the women surveyed reported having tried lubricant or moisturizers to treat the symptoms. Further, 52% of the women surveyed were unaware of local estrogen therapy as an effective treatment options for their vaginal atrophy symptoms.
**Vulvar Changes and Conditions**
In response to estrogen loss, the vulva loses most of its collagen and adipose tissue. The vulvar tissue loses its ability to retain water, and becomes flattened and thin. Secretions also diminish. The fold of skin covering the clitoris atrophies, exposing the gland to irritation from clothing, prolonged sitting, and sexual contact.

**Table 2: Vulvar conditions**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Description</th>
<th>Result(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic atrophic vulvitis</td>
<td>Repeated irritation of atrophic tissue</td>
<td>Causes the vulva to become itchy, scaly, red with fissuring and slight bleeding</td>
</tr>
<tr>
<td>Kraurosis Vulvae</td>
<td>Severe atrophy of the vulva in an advance state</td>
<td>Results in narrowing of the vaginal orifice and excessive shrinking of the labia.</td>
</tr>
<tr>
<td>Vulvar dystrophy</td>
<td>Formation of whitish-looking plaques over large areas of the vulvar tissue or in multiple discrete site</td>
<td>Can precede the development of cancer</td>
</tr>
</tbody>
</table>

Note: Premarin Vaginal Cream and Estragyn are indicated for the treatment of kraurosis vulvae; Estring and Vagifem® 10 are not indicated for use in this condition.

**Mini Quiz:**

1) **Name a change in appearance of the vagina seen in vaginal atrophy.**

2) **What percentage of women with symptoms of vaginal atrophy will seek medical help?**

**Clinical Evaluation of Urogenital Health**
Clinical evaluation of urogenital health in menopausal women is done through a pelvic examination. Due to a loss of rugae, the postmenopausal vagina is shortened, smooth, and narrowed. The vulvovaginal epithelium is comparatively pale, thin, and friable. Submucosal petechial hemorrhages (pinpoint, nonraised, round, purple-red spots caused by submucous hemorrhage) may be visualized.

Decreased tissue elasticity may cause narrowing and limited vaginal mobility. Pelvic floor relaxation with prolapse of the vaginal walls or uterus is often present. Urethral prolapse can occur with resultant postmenopausal bleeding. Like the vagina, the urethral and bladder mucosa appear pale and thin.

Laboratory markers of vaginal atrophy include a vaginal pH greater than 5.0 and a change in the maturation index of the vaginal wall towards a predominance of
parabasal cells, reflecting superficial thinning of the mucosa. Culture of the vagina may reveal growth of enteric organisms not normally found in the vagina.

**Mini Quiz:**

1) **How is urogenital health evaluated?**

2) **What changes may be observed during clinical evaluation of the vagina?**

**VAGINAL ATROPHY TREATMENT**

The primary goals of vaginal atrophy management are to alleviate symptoms and to reverse atrophic anatomic changes. First-line therapies for women with vaginal atrophy include non-hormonal vaginal lubricants and moisturizers, as well as continued sexual activity.

**Lifestyle Modification**

Since a decline in estrogen levels is the primary etiology behind vaginal atrophy, lifestyle factors that accelerate this decline should be avoided. The following are recommended to minimize the risk of developing vaginal atrophy symptoms:

- Smoking cessation should be encouraged.
- Continued regular vaginal coitus provides protection from urogenital atrophy by increasing the blood flow to the pelvic organs.
- Masturbation has also been shown to increase genital blood flow in menopausal women and may help maintain urogenital health.

**Natural Products**

Research has failed to demonstrate any beneficial effect of dietary estrogen or supplements, such as black cohosh or dong quai, on vaginal atrophy.

Very limited short-term data (30 women for a 3-month period) showed some efficacy on symptoms and cytology for phytoestrogen inserted vaginally. Vitamin D supplementations (calcitriol, 0.5 μg/d) for 3 months in 30 women showed benefits on cytology only and no impact on symptoms compared to placebo.

**Vaginal Lubricants & Moisturizers**

Current SOGC treatment guidelines state that “vaginal lubricants and moisturizers may be recommended for subjective symptom improvement of dyspareunia.”

*Vaginal lubricants* can alleviate dryness and discomfort however they do not reverse the changes associated with vaginal atrophy which is one of the primary goals of treatment. There are several lubricants currently available in Canada (KY Jelly, AstroGlide, etc.). While vaginal lubricants can be used to decrease immediate irritation during coital activity, there is no evidence that these products have any long-term therapeutic effect. As the name implies, they provide lubrication.
Vaginal moisturizers will bring moisture to the vaginal lining and thereby bring some relief; moisturizers have longer effects than lubricants. In Canada, moisturizers typically contain polycarbophil gel (Replens) or hyaluronic acid (Gynatrof gel, RepaGyn). There is no scientifically robust data that exists to support the efficacy of hyaluronic acid, and neither lubricants nor polycarbophil gel would be expected to yield vaginal cytomorphologic or pH improvements or reduce the lower urinary tract symptoms associated with urogenital atrophy such as dysuria and urinary urgency.

**Local Estrogen Treatment**

Exogenous estrogen therapy (ET) has multiple effects on the vagina, including increased blood flow, improved epithelial thickness, reduced pH, and increased secretions. Intravaginal estrogen therapy can be used for vaginal dryness either alone or in addition to systemic estrogen replacement therapy. Up to 40% of women receiving systemic therapy do not get an adequate effect of estrogen on the vaginal mucosa. The 2014 SOGC Managing Menopause Guideline states:

*When the only complaint is lack of efficacy of systemic treatment for vaginal atrophy, adding a vaginal preparation of estrogen is the first choice.* (page S54)

The following local estrogen therapy options are available in Canada:

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Tablet</th>
<th>Creams</th>
<th>Ring</th>
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<tbody>
<tr>
<td><strong>Brand Name</strong></td>
<td><strong>Vagifem® 10</strong></td>
<td><strong>Premarin Vaginal Cream</strong></td>
<td><strong>Estragyn</strong></td>
</tr>
<tr>
<td><strong>Estrogen Type</strong></td>
<td>Estradiol</td>
<td>Conjugated estrogen</td>
<td>Estrone</td>
</tr>
<tr>
<td><strong>Estrogen Dose</strong></td>
<td>10 µg (or 0.01 mg)/tablet</td>
<td>0.625 mg/g</td>
<td>0.1% w/w †</td>
</tr>
<tr>
<td><strong>Recommended Dosage</strong></td>
<td><strong>Initial:</strong> 1 tablet daily for 2 weeks</td>
<td><strong>Low dose:</strong> 0.5 g twice weekly</td>
<td>2-4 g daily for 25 days, 5 days off, and repeat</td>
</tr>
<tr>
<td>Maintenance: 1 tablet twice weekly</td>
<td><strong>Max dose:</strong> 0.5-2 g daily for 21 days, 7 days off, and repeat</td>
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</tr>
<tr>
<td><strong>Estrogen Delivery Over One Year at Recommended Dosage</strong></td>
<td>1.14 mg in the first year, and 1.04 mg in subsequent years</td>
<td>32.5 mg and up to 342.5 mg at max dose</td>
<td>610 mg and up to 1220 mg at max dose (Although not recommended, some HCPs may prescribe as low as 0.5 g daily, which equates to 152.5 mg of estrone delivered annually)</td>
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† 0.1% w/w = weight/weight meaning there is 0.1 g of estrone/100 g of cream or 1 mg/g of cream
Only Vagifem® 10, Estring and Premarin Vaginal Cream are recommended by the SOGC as effective treatments for vaginal atrophy. Recommendations are supported by randomized controlled studies demonstrating safety and efficacy. There is no clinical trial supporting the safety and efficacy of Estragyn for vaginal atrophy.

**Systemic Absorption of Local Estrogen**

Estrogen placed in the vagina can have systemic effects if given in sufficient quantity. Very low doses are needed in the vagina to reverse atrophic change, so systemic absorption can be limited. That said, when the vaginal mucosa is most atrophic is also when it is most permeable, so absorption may occur at the beginning of treatment until the mucosa matures and becomes less permeable. In a low dose, it may be transiently absorbed in the first 7 to 14 days. After the first two weeks of treatment, the serum estradiol concentration tends to return to pre-treatment levels and remains low on serial assay over 12 weeks.

With Vagifem® 10, containing only 10 μg of estradiol, the absorption is restricted to less than 24 hours (i.e., after a single initial dose) indicating that there is minute (and insignificant) systemic absorption with this dose. Systemic absorption and pharmacokinetics of Vagifem® 10 will be addressed in Module 3.

Many studies of vaginal estrogen (all formulations) have shown no evidence of endometrial proliferation after 6 to 24 months of use; therefore, in general, concomitant progestogen therapy or endometrial surveillance is not recommended in asymptomatic (nonbleeding) women. After conducting their population based case-control study of 789 cases of endometrial cancer, Weiderpass et al concluded that vaginal low potency ET did not increase the risk of endometrial cancer. Endometrial safety of Vagifem® 10 will be addressed in Module 3.

**Measuring the Effectiveness of Local Estrogen Treatment**

**Objective Measures:**

**Vaginal Cytology**

Estrogen treatment causes vaginal mucosal maturation, shifting the atrophic mucosa from a predominantly parabasal cell population to a superficial cell population, based on cytologic evaluation. The restoration of normal vaginal cytology is frequently used as an objective outcome measure to assess the hormonal treatment effect.

**pH**

Vaginal estrogen treatment restores vaginal pH to premenopausal levels by reestablishing the normal number of lactobacilli in the vaginal flora. Randomized controlled trials of vaginal estrogen treatment often evaluate pH as an outcome. Compared with baseline, all vaginal estrogen preparations significantly decreased pH from pretreatment values of approximately 6.0 to less than 5.0.

**Subjective Measures:**

**Vaginal Appearance**

Some investigators use improvements in gross vaginal appearance to assess the therapeutic efficacy of vaginal estrogen treatment. As with the symptoms of
vaginal atrophy, the signs (e.g., pallor, dryness, friability, petechiae) are significantly improved with all vaginal estrogen preparations.

**Assessment of Vaginal Atrophy Symptoms**
Prior to 2003, double-blind, placebo controlled trials of estrogen treatment used different symptom outcome measures. In 2003, the FDA produced a document for industry giving guidance on the evaluation of estrogen product for vaginal atrophy, which requires the following symptom evaluation:

- Mean change from baseline to week 12 in the moderate to severe symptom that has been identified by the patient as being the most bothersome to her

The FDA guidance document also sets out requirements as to patient inclusion criteria for products seeking indication of treatment of moderate to severe symptoms of vulvar and vaginal atrophy. Study participants should be enrolled if they have self-identified at least one moderate to severe symptom that is the most bothersome to her, have no greater than 5 percent superficial cells on a vaginal smear, and have a vaginal pH > 5.0.

**Mini Quiz:**

1) What is the limitation of treatment when using vaginal lubricants or moisturizers for vaginal atrophy?

2) Which treatment can reduce the frequency of urinary tract infection?

3) What does the FDA recommend regarding symptom evaluation for vaginal atrophy?

4) What four assessments are used to show the effectiveness of vaginal estrogen in vaginal atrophy?

5) What are the primary goals of vaginal atrophy treatment?