

Ecology and Health of the Menopausal Vagina

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The study of the health of the menopausal vagina does not have a long history. It is only within the past 100 years that mean life expectancy for the majority of women reached the average age at which women experience menopause. For millions of years, the primary function of this complex organ has been to facilitate intercourse via the collection and protection of sperm at its apex, permitting entry into the upper genital tract to accomplish fertilization. No less important is the vagina's function to protect the developing fetus from invasion of numerous endogenous and exogenous bacteria present in or near the lower genital tract, through the maintenance of an acidic environment inhospitable to potential pathogens.¹ Now that most women are living two to three decades into menopause, the postmenopausal vulva and vagina have become the focus of more scientific inquiry. This new focus on the ecology and health of the menopausal vagina will lead to a greater understanding of this important phase of women's health.

Although the significance of the premenopausal vagina to the survival of the species is undeniable, the social, behavioral and economic implications of vaginal health and

disease in menopause have been poorly studied relative to the rapidly increasing percentage of the female population now over age 50.² It is generally thought that the vagina has

limited functionality in menopause; however, it is not only an essential organ for sexual pleasure and intimacy, but also continues to play a variety of roles with regard to health maintenance. An estrogen-deficient vagina can result in obvious problems, such as discomfort and dyspareunia, and also can lead to an environment that promotes the growth of abnormal flora, which may lead to a variety of infections, including frequent urinary tract infections and a potential for renal compromise. Loss of vaginal muscular tone may lead to cystocele, rectocele, prolapse and loss of urinary or fecal continence.^{3,4} Finally, environmental, genetic and infectious factors in menopause may lead to dysplasia and carcinoma of the urogenital tract.⁵⁻⁹ One of the still poorly understood effects of menopause is highlighted by the differential effects of the human papilloma virus (HPV). HPV causes cervical carcinoma, both pre- and postmenopause, whereas vulvar and vaginal HPV-related cancers are predominantly postmenopausal occurrences.

With a recent surge in interest in menopausal vaginal health, much

work has been done clinically to help menopausal women manage many of the anatomic, dermatologic and dysplastic lesions of the aging vulva and vagina. Urogynecology and reconstructive pelvic surgery is a newer and important subspecialty of obstetrics and gynecology that deals with many of the anatomic issues surrounding prolapse and incontinence. Residents and practicing clinicians alike are now well versed in the mantra of biopsy for all postmenopausal vulvar pruritis. Recent advances in topical treatments for atrophic vaginitis, lichen sclerosis and other dermatopathologies have also made it easier to treat these lesions.

Still largely overlooked, however, is the urogenital flora in menopause. Once thought to be relatively sparse and unimportant, the vagina is now being recognized as a complex and dynamic environment. Recent advances in molecular bacterial diagnostics have demonstrated many novel bacterial species that interact with other organisms and the menopausal vagina. The menopausal vaginal epithelium, also once thought of as a thinning and poorly functioning barrier, is now known to act and react with our increasingly vast array of pharmacologic interventions.

The remainder of this article focuses on the increasing evidence of the dynamic and interactive nature of the microbial ecology of the menopausal vagina and vulva.

Vaginal Microbiology

The vagina is composed of three layers: the vaginal epithelium, a muscular layer and, finally, an outer fibrous layer derived from the pelvic

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fascia. The vaginal epithelium consists of stratified squamous cells (and thus is not a true mucosa), and contains the greatest number of nuclear estrogen-binding sites. With the initiation of estrogen stimulation at menarche, superficial cells predominate over parabasal cells. The mature superficial cells are thought to enhance the protective barrier. Thus, as less mature parabasal cells increase as women approach menopause, a thinner, less protective layer remains.

The microbiology of the vagina varies greatly during a woman's life span, due most directly to the influence of sex steroids on lower genital tract tissues. Bacterial growth is essentially a simple mathematical equation: the number of organisms present (based on inoculum and available food sources such as glycogen) divided by the host's immune responses. The relative deficiency of glycogen in the premenarchal and menopausal vagina leads to quanti-

tatively fewer numbers of bacteria present relative to those present during reproductive years.

Lactobacillus and vaginal pH. Most bacteria require an environment rich in nutrients, warmth and moisture to grow. In the laboratory, this environment is supplied by growth media and incubators. In the living human, moisture comes in the form of vaginal secretions, which normally consist of a vaginal transudate that includes desquamated epithelial cells, cervical mucus and endometrial fluid. In normal vaginal secretions, *Lactobacillus* species proliferate. Lactobacilli use the glycogen from desquamated superficial cells as a substrate, and convert glucose to lactic acid and hydrogen peroxide. The lactic acid and hydrogen peroxide result in a low vaginal pH (approximately 4.2), which prohibits growth of most pathogenic bacteria. With bacterial infections, an increase in organic acid byproducts results in an increasing pH, which causes lactobacilli to decrease in numbers, while facultative and anaerobic organisms proliferate. In menopause, *Lactobacillus* numbers decrease more than 99% from levels found in the premenopausal years (from 10^{7-8} to $<10^5$).¹⁰ As the glycogen food source for bacteria is rapidly utilized by faster-growing aerobic pathogenic bacteria, the vaginal pH increases to approximately 5.0-6.0, whereupon the *Lactobacillus* species is replaced with bacterial species from the perineum.^{11,12} Freedman followed 300 postmenopausal women after cessation of hormone therapy and found that 290 women had a pH greater than 4.5 within 6 to 12 months.¹³

Restoration of estrogen with exogenous replacement will slowly decrease the pH to ≤ 4.5 , permitting the regrowth of *Lactobacillus*. However, the pathogenic species that replace the lactobacilli may not relinquish their dominance of the vaginal flora, occasionally resulting in symptoms of vaginal discharge, odor or irritation.

Diagnosis of Menopausal Vaginal Infections

Despite the belief that the lack of estrogen, and therefore a decrease in glycogen, in the menopausal vagina causes a significant decrease in bacterial growth, it has become apparent that various species can inhabit the vagina and cause symptoms. Diagnosis can be more complicated because some of the criteria utilized to diagnose vaginitis, such as elevated pH, are altered in menopause.

Work-Up. Work-ups of vulvar and vaginal symptoms should begin with a thorough history of the woman's menopausal status, including how long the woman has been menopausal and her history of exogenous hormone use. Complaints of postmenopausal vaginal bleeding and vulvar pruritis always necessitate a cancer evaluation, regardless of other vaginal symptoms. If discharge is the primary symptom, a recent change in medications—especially the use of antibiotics, exogenous estrogen or selective estrogen-receptor modulators (SERMs)—should be investigated.

A sample should be obtained for pH and wet prep examination. A Whiff test should also be performed. An elevated pH in premenopausal women is abnormal and is often in-

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dicative of a bacterial or parasitic infection; however, pH is generally elevated in menopause and thus is not as helpful. A low or normal pH in menopausal women is generally the result of the influence of endogenous or exogenous estrogen, or perhaps SERM use. Recent trials of new SERM agents have utilized lowered pH as a primary outcome.^{14,15} A low pH may also be the result of self-medication with an acidic topical gel, cream or douching preparation prior to the office visit, and the patient should be asked if such a product has, indeed, been used. With examination of the wet prep, the ratio of superficial to parabasal cells can easily be noted. Even if another infection is diagnosed, the coexistence of atrophic vaginitis should be addressed during or after successful treatment of the current infection.

In the absence of a severe bacterial or parasitic infection, there generally will be a decrease or absence

of *Lactobacillus*-like morphotypes and other bacteria. If yeast morphotypes are absent and the vagina is thin and pale with poor rugae, then a diagnosis of atrophic vaginitis may be considered and treatment initiated. If the patient's examination demonstrates adequate estrogen response and many bacteria and white blood cells are present, she most likely has bacterial vaginitis (not bacterial vaginosis), as the denuded epithelium, elevated pH and lack of lactobacilli all favor bacterial growth. Symptoms of vaginal irritation, but not itching, make a primary diagnosis of yeast infection less likely, and further evaluation is necessary to identify the offending pathogen.

Postmenopausal vaginal infections. The following are some of the vaginal infections clinicians should expect to encounter in their postmenopausal patients.

- *Desquamative inflammatory vaginitis (DIV).* This less common form of vaginitis can cause symptoms of yellow or green vaginal discharge, burning and dyspareunia. It appears to be more common in peri- and postmenopausal women, and diagnosis can be made with an elevated vaginal pH, increased vaginal leukocytes and parabasal cells, and vaginal and vulvar erythema with a negative Whiff test. The best treatment is generally believed to be 2% topical clindamycin cream for 14 days, as group B streptococci are often associated with DIV.¹⁶
- *Candida infections.* While it is generally believed that postmenopausal women rarely suffer from candidal vulvovaginitis,^{17,18}

ongoing research has demonstrated that the menopausal vagina becomes increasingly susceptible to *Candida* infections, with a significant increase after 5-10 years of estrogen deprivation.¹⁹ While pruritis will often be a symptom with *Candida* infections, persistent pruritis after antifungal treatment necessitates a vulvar biopsy to rule out dysplasia or other dermatopathology. If no pseudohyphae are noted on wet prep examination, but the clinical diagnosis of candidal vulvovaginitis is likely due to signs, symptoms and vaginal inspection of the discharge, a non-albicans species such as *Torulopsis (Candida) glabrata* should be suspected and treatment initiated with a topical (not oral) antifungal.²⁰ Oral fluconazole is not helpful for non-albicans species.²¹ The topical agents with the best antifungal activity against non-albicans species are prescription terconazole and nonprescription tioconazole. Boric acid is very helpful and is the gold standard for treatment of non-albicans species in premenopausal women, but is often poorly tolerated in women with coexisting atrophic vaginitis.¹⁸ Therefore, when a non-albicans species is present, concomitant estrogen therapy (ET) with these antifungal agents may be helpful in decreasing the likelihood of recurrences of this difficult-to-treat fungal pathogen.

- *Viruses*. While new herpes simplex infections are uncommon in postmenopausal women, HPV infections most likely represent a persistent infection, which can be a cause of concern. As part of the

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Postmenopausal Estrogen/Progestin Interventions trial, Smith and colleagues²² demonstrated a cumulative rate of HPV of 34% over 7 years. Of those positive for HPV, 24% had high-risk oncogenic types, which are associated with cervical, vulval and vaginal cancer.

Treatment of Menopausal Vaginal Infections

Treatment of an underlying atrophic vaginitis is often necessary to achieve long-term resolution of bacterial or fungal infections of the vagina and vulva.

Estrogen therapy. ET, preferably administered topically, is often helpful after treatment of the pathogen or pathogens is completed, as relapse is likely to occur unless the vaginal epithelium is enhanced to become an effective barrier again. Embryologically, the outer vagina, vulva, urethra and trigone are derived from the urogenital sinus, and thus are very responsive to ET. The inner vagina is derived from the Müllerian system and contains a

lower concentration of estrogen receptors.^{23,24} While treatment of isolated atrophic vaginitis can be accomplished with systemic estrogen, all topical estrogen preparations indicated for treatment appear to function equally well,²⁵⁻²⁷ and have the important benefit of delivering a lower systemic dose to the patient.

Finally, while ET reduces vaginal pH to premenopausal levels, further decreases can be accomplished with sexual activity.¹¹

SERMs. While tamoxifen and raloxifene have not demonstrated effectiveness in the treatment of atrophic vaginitis, newer SERMs appear to be helpful with vaginal and vulvar symptoms. Multicenter trials of lasofoxifene have demonstrated a significant improvement in vaginal atrophy.²⁸ Tibolone, a synthetic nortestosterone derivative, has selective estrogen, progesterone and androgen activity. It appears to also have beneficial effects in the vagina,²⁹ and has been widely used in Europe for years. Neither agent is available in the United States, but similar agents that confer similar results will, it is hoped, be available in the United States in the near future.

Conclusions

As women live longer, vaginal symptoms during the postmenopausal years will become a more common feature of clinical practice. New pharmacologic tools, the expanded interest in vaginal moisturizing and, hopefully, new SERM agents will both directly and indirectly affect the vagina and vulva. This greater understanding of the menopausal vulva and vagina will contribute to

the continued health of menopausal women. ■

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This article includes discussion of off-label use of medications.

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