Menopause, the cessation of menstruation for 6 to 12 months, is a natural progression of life for women (O’Toole, 2003). The average age of menopause is 51 years of age (Hall, 2004). Today, there are 42 million women over the age of 50. By 2010, 52 million women will reach this age; 20 million of whom will develop vaginal atrophy (Notelovitz, 1997). Add to these numbers women who receive anti-estrogen medication to prevent recurrence of breast cancer and the number of women with vaginal atrophy increases (Vardy et al., 2003).

Menopausal changes are influenced by fluctuating levels of estrogen that gradually diminish until estrogen levels are so low there is cessation of menses. Troublesome symptoms of menopause can include disrupted sleep, vasomotor instability (hot flushes), and irritability (Cothran & Engberg, 2004). The severity of these symptoms varies. Some women experience palpitations, headaches, memory difficulties, and depressed mood. Other subtle changes may go unnoticed by health care providers, such as vaginal atrophy, until there are presenting symptoms of urinary incontinence (UI), dyspareunia (painful intercourse), or frequent urinary tract infections (UTIs).

Attention to the signs and symptoms of vaginal atrophy are not heeded by many practicing clinicians. Vaginal atrophy, a prevalent consequence of urogenital aging, affects 50% of menopausal women (Notelovitz, 1997). Clinicians may not routinely question patients about symptoms of vaginal atrophy, such as vaginal itching or irritation, yeast infections, frequent UTIs, UI, or dyspareunia. This may also be compounded by the fact that many women underreport these symptoms (Johnston & Farrell, 2004).

Urogenital changes, whether subtle or dramatic, can have a significant effect on a woman’s comfort and may affect continence. For many women, there are concerns about the risks and benefits of oral estrogen hormone therapy (EHT) and EHT used with progesterone or progestin (for example, hormone replacement therapy [HRT]). Also in question is the efficacy of EHT/HRT in preventing heart disease (if initiated early in peri-menopausal women) and its use in maintaining bone health (Phillips & Langer, 2005; Speroff, 1996). Recently, the large Women’s Health Initiative study regarding the untoward effects of HRT has caused confusion for clinicians and patients in determining the efficacy of using oral therapies to treat menopausal symptoms (LaCroix, 2005; Speroff, 1996; Stefanick, 2005). In addition to oral therapies, a wide variety of vaginal estrogen preparations are also available (see Table 1).

An overview of hormonal changes that typically occur during menopause, its effect on vaginal health, and recommendations for evaluation and treatment of vaginal atrophy are discussed.

Anatomy and Physiology Of the Urogenital Tract

The anatomy of the urogenital tract is made up of the pelvic floor muscles, urethra, and vagina. The approximation of these structures to one another may be directly impacted by the effects of aging and trauma through childbirth. The lower two-thirds of the urethra are inseparable and an integral part of the anterior vaginal wall which arises from the same embryonic origin (Losif,
The major structures of the female external genitalia (vulva) include the mons pubis, labia majora and minora, clitoris, vestibule, Skene and Bartholin glands, and urethral meatus. Estrogen causes fat deposits under the skin of the mons pubis. The internal genitalia are comprised of the vagina, uterus, fallopian tubes, and ovaries. Adjacent to the vagina is the urethra and located superiorly is the bladder. The external and internal genitalia are predominately affected by the hormone estrogen (Deneris, Huether, & Robinson, 2004). Major support ligaments are the pubococcygeus muscle and musculature of the pelvic floor which includes the levator ani.

Estrogen is present in all of the muscles and ligaments with the exception of the levator ani and dome of the bladder (Blakeman, Hilton, & Bulmer, 1996). Squamous endothelial tissue is most directly influenced by estrogen. Due to the arterial rich and venous meshes of the urethra and anterior vagina, hormones are transferred easily, an effect referred to as counter transfer (Cinicelli et al., 2001). This exchange between arterial and venous blood may be responsible for adequate response with low-dose topical estrogen without causing endometrial proliferation.

Circulating endogenous estrogen, present in higher levels before menopause, affects the maturation of vaginal tissues. Estrogen receptors are absent in the urothelial tissues but are present in the squamous epithelium and uterosacral ligaments throughout the lower urinary tract. These receptors have an effect on the proximal and distal urethra, vagina, and trigone of the bladder in the form of 17β-estradiol (ER-β). ER-β is a recently identified glycoprotein (Blakeman et al., 1996). Estrogen increases urethral resistance, raises the sensory (proprioceptive) threshold of the bladder, increases adrenoreceptor sensitivity in the urethral smooth muscle, and promotes β-adrenoreceptor-mediated relaxation of the detrusor muscle (Robinson & Cardozo, 2003; Vardy et al., 2003).

Much of the research determining the role of hormonal influence on the lower urinary tract has been done by Blakeman et al. (1996). They found that progesterone and androgen receptors are present in the lower urinary tract but not as consistently prevalent as estrogen receptors. Progesterone receptors are mostly found in subepithelial tissues, with lower progesterone levels found in women not taking HRT.

### Neurologic Control

Control of the lower urinary tract is under the influence of the sympathetic, parasympathetic, and somatic nervous systems (Blok, Willemsen, & Holstege, 1997). These signals arise from innumerable areas of the brain and spinal cord. In the brain, there is the detrusor motor area (cortex), limbic system in the septal region, facilitatory system in the thalamus and hypothalamus, and the detrusor reflex and sphincter coordination in the brainstem micturition area (Blok et al., 1997). The sacral nerves in the spinal cord influence the pudendal nerves of the pelvic floor. Estrogen receptors are present in all these areas. Estrogen can directly affect detrusor function through muscarinic receptors and calcium ion movement into cells (Elliott, Castleden, & Middrog, 1992). There is a reduction in the amplitude and frequency of spontaneous rhythmic detrusor contractions in the presence of estradiol (Shenfield, Blackmore, & Morgan, 1998).

### Table 1. Vaginal Preparations of Estrogens in the Treatment of Atrophy

<table>
<thead>
<tr>
<th>Vaginal Preparation</th>
<th>Strength</th>
<th>Treatment Regime</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conjugated equine estrogen* (Premarin®) cream</td>
<td>0.625 mg/gram</td>
<td>1 gram vaginally 3 x week</td>
<td></td>
</tr>
<tr>
<td>Estradiol vaginal cream (Estrace®)</td>
<td>2 mg/gram</td>
<td>1 gram vaginally 3 x week</td>
<td></td>
</tr>
<tr>
<td>Estradiol vaginal ring* (Estring®)</td>
<td>7.5 μg daily release</td>
<td>Retained in vagina and replaced every 3 months</td>
<td>Slow release dose of 7.5 μg daily</td>
</tr>
<tr>
<td>Estriol vaginal cream**</td>
<td>0.5 mg/gram</td>
<td>2 x week</td>
<td>Compounded by pharmacist</td>
</tr>
<tr>
<td>Estradiol vaginal tablet* (VagiFem®)</td>
<td>25 μg/tablet</td>
<td>2 x week</td>
<td></td>
</tr>
</tbody>
</table>

* Recommended by the Society of Obstetricians and Gynecologists Joint Committee as effective therapy (Johnston & Farrell, 2004).
** Not approved by the Federal Drug Administration
Age-Associated Changes

The physical examination of women with atrophic tissues typically reveals thinning pubic hair, narrowing vaginal introitis, petechiae of vaginal tissues, and loss of ruga (see Figure 1). The vaginal pH is generally greater than five. The presence of a caruncle may also be indicative of atrophic vaginitis (see Figure 2). In clinical trials, maturation indexes are used to determine the depth of epithelial tissue with thicker epithelium indicating less atrophy (Ayton et al., 1996).

Elderly women have less vaginal estrogen since there is less circulating estrogen. In postmenopausal women, ER-β is absent in vaginal tissues. Bladder function also changes with age. The loss of estrogen in tissues can cause a reduced urinary flow rate, increased urinary residual volume, higher filling pressures, reduced bladder capacity, and lower maximal voiding pressures (Robinson & Cardozo, 2003). Urethral closure and pressure is a main component of continence. However, with age the urethral pressure decreases (Beisland, Fossberg, Moer, & Sander, 1984; Cothran & Engberg, 2004).

Vaginal atrophy results when there is less estrogen present in genital tissues of post-menopausal women. The increase in vaginal atrophy due to lower circulating estrogens contributes to vaginal dryness, loss of pelvic support with resulting prolapse, decreased tissue elasticity with resulting dyspareunia or pressure to void frequently, and urogenital discomfort (Eriksen & Rasmussen, 1992; Notelovitz, 1997).

Oral Estrogen’s Effect on Continence

Estrogen is present in the urogenital tract and is deficient after menopause. Generally UI affects one-third of noninstitutionalized adults over age 65, with 25% to 30% experiencing incontinence episodes (Baum, 2006). UI, especially urge incontinence, increases with age (Holst & Wilson, 1988). Grady (2001) found worsening symptoms of UI in women using daily oral doses of conjugated equine estrogen (CEE) (Premarin®) 0.625 mg and medroxyprogesterone (MPH) (Provera®). This randomized 4-year study included 2,763 women, with intact uteri, who were less than 80 years old. When compared to placebo, results between groups showed UI symptoms that occurred more than once a week improved more (26%) in women not on HRT compared to 21% improvement for those who were on HRT. Moreover, there was a clinically significant worsening of symptoms in 39% of subjects receiving HRT compared to 27% in the placebo group (p<0.1).

Two additional studies highlight this point. Ouslander and colleagues (2001) investigated 32 women in a LTC facility with an average age 88 years. Subjects were randomly assigned to a treatment group of oral estrogen (CEE 0.625 mg/MPH 2.5 mg) or a placebo group. Although there were some positive clinical findings in the treatment group, there was no statistical difference in UI episodes, bacteriuria, or vaginal cultures as compared to the placebo group.

Another study reported the effect of a daily dose of oral estrogen (CEE 0.625 mg/MPH 2.5 mg) on 1,525 post-menopausal women (age 50 to 79) with heart disease (Hendrix et al., 2005). The researchers noted the overall risk
of developing UI (stress and urge types) increased over 1 year from baseline.

**The Effect of Vaginal Estrogen on Continence**

A review of the literature indicates inconsistent findings on use of vaginal estrogen to decrease UI symptoms in post-menopausal women. Ouslander, Cooper, and Godley (1999) studied UI in frail, older women. They concluded that improvement in UI may be related to other interventions concomitant with vaginal estrogen supplementation, such as behavioral therapies or other pharmacologic treatments.

Fantl, Wyman, Anderson, Matt, and Bump (2002) compared clinical and urodynamic variables of 72 post-menopausal women 55 years of age. Forty-nine women were on no estrogen supplementation and 23 women were either on oral supplementation or a vaginal preparation. Of the women on supplementation, 20 were taking oral supplementation, two were using a vaginal preparation, and one was on both an oral and vaginal preparation. Results demonstrated no statistical improvement in UI whether on no estrogen supplementation versus oral supplementation, or a vaginal preparation. The study did show, however, a decrease in nocturia and fewer episodes of urinary frequency and urgency.

Eriksen and Rasmussen (1992) studied the effect of vaginal estrogen in the tablet form of 25 μg 17β-estradiol (VagiFem®) in 164 women with subjective symptoms of vaginal atrophy. Subjective symptoms included itching, burning, dyspareunia, and urological symptoms of frequency, dysuria, and urgency. After 12 weeks of treatment, 62.8% of the treatment group experienced improvement in symptoms compared to 32.4% in the placebo group.

**Vaginal pH and Urinary Tract Infection**

Urinary tract infections may lead to an increase in UI. This is especially difficult to determine in the older female population residing in long-term care (LTC) facilities because of the overall high rate of UI (Maloney, 2002). Since the glycogen content of vaginal tissues is increased in the presence of estrogen there is a more acidic environment which allows lactobacillus to be the most predominant bacterium present in the vagina (Maloney & Oliver, 2001). This acidic environment discourages the growth of pathogenic bacteria. The pH of non-atrophic vaginal tissue is less than 5 and atrophy aggrases until the vagina becomes more alkaline, or at a pH of greater than 6 (Davila et al., 2002; Johnston & Farrell, 2004).

Eriksen (1999) investigated the use of topical estrogen in the form of an estradiol vaginal ring (Estring®) in the prevention of UTI. Estring is a small silicone vaginal ring impregnated with 17β-estradiol. The 17β-estradiol is released slowly by body temperature over 3 months. A total of 108 women in Norway (age range 47-87 years) with recurrent UTIs were evaluated to determine if the treatment group had fewer recurrences of UTI than the control group. After 36 weeks, Eriksen (1999) concluded the majority of UTI recurrence occurred before week 12 which was not adequate time for the pH to stabilize. However, the treatment group had a longer interval before recurrence than the control group.

Escherichia coli, a common UTI pathogen, can flourish in an environment of increased pH (Maloney & Oliver, 2001). A study of vaginal pH levels (N=258 post-menopausal women; mean age 83), compared women using topical CEE vaginal cream for 6 weeks (n=213) with a no treatment group (n=45) (Maloney & Oliver, 2001). Results showed the treatment group had a significant decrease in pH (more acidic) whereas no change was noted in the pH of the nontreatment group (n=45). Although the study was limited by size and duration of treatment, the authors concluded that the decrease in vaginal pH may support an association between preventing recurrence of UTIs if the vaginal pH is more acidic. In another small placebo controlled study (n=32) of incontinent, female, LTC patients, a dramatic effect on pH was noted using the estradiol vaginal ring (Estring) for 1 month. In addition, vaginal pH fell from 6.4 to 4.2 during that time (Ouslander et al., 1999).

**Case study: The effect of estrogen on preventing UTI.** An 86-year-old female, after residing 3 years in a LTC facility, began experiencing recurrent UTIs every other month. The pathogen consistently was Escherichia coli. Staff attention to perineal care and toileting did not relieve the problem. A continence specialist was involved in the care and determined there was no significant post-void residual volume. A treatment regime of estradiol vaginal cream (Estrace) was implemented. The patient initially did not cooperate with administration of the medication, as it was upsetting to her. After several months, the medication route was changed to the estradiol vaginal ring (Estring). This was acceptable to the patient, and there has been no UTI recurrence over the last 6 years.

**Comments.** This case is supported by the findings previously mentioned by Eriksen (1999). It is also important information to consider when developing an intervention in clinical practice for patients presenting with recurrent UTIs. The introduction of vaginal estrogen, predominately in the form of an Estring, may be responsible for the decreased UTI recurrence in this case study. The estradiol vaginal ring was preferred by this patient as it required changing only once every 3 months and preserved her modesty. The nursing staff also appreciated the time-saving aspect of this treatment.
Unopposed Estrogen

There is concern about uterine endometrium with the use of topical estrogen in women who have an intact uterus (Nothnagle & Taylor, 2004). A number of studies reviewed by Suckling, Lothaby, and Kennedy (2006) in the Cochrane Database have addressed this topic. The dose of estrogen is low enough in all vaginal creams, rings, and vaginal tablets (VagiFem®) to not cause excessive proliferation and not require the use of a progestin or progesterone to prohibit proliferation of the uterine lining (Suckling et al., 2006). Administration of a vaginal preparation results in one-half to one-fourth the serum estrogen values compared to equivalent oral doses (Grow, 2002). As noted by Ayton et al. (1996), consideration must be taken into account regarding the short intervals of treatment in the studies. Longer treatment regimes should be used with caution, keeping in mind the possibility of endometrial proliferation in women with an intact uterus. The preferred method of delivery to the vaginal tissues was the tablet form (VagiFem), or the estradiol vaginal ring (Estring) because of the ease of use. Both do not cause endometrial proliferation (Ayton et al., 1996; Eriksen, 1999).

Although not approved by the Federal Drug Administration, estriol vaginal cream does not stimulate the endometrium nor does it convert to estradiol in the body (Eckler, 2004; Yoshimura & Okamura, 2001). The pharmacokinetics of this preparation may make it an option for women who have had or are at high risk for breast cancer or endometrial cancer. In a prospective study (Losif, 1992), only slight endometrial changes were noted after 8 to 10 years of topical vaginal estriol use. Another larger randomized study comparing the estradiol vaginal ring (Estring) and estriol cream showed no difference in adverse effects (Barentsen, van de Weijer, & Schram, 1997). This included no withdrawal bleeding over a 12-week treatment period. Likewise, a study by Heimer and Englund (1992) showed no withdrawal bleeding before or after 6 weeks of treatment with estriol vaginal cream (0.05 mg) twice weekly.

Practice Recommendations

The risks and benefits of vaginal estrogen use, whether in tablet, cream, or vaginal ring preparation, should be carefully reviewed with the patient and treatment determined on an individual basis. Clinical practice guidelines on the detection and management of vaginal atrophy were developed by Canada’s Joint Commission of Clinical Practice Gynaecology and Urogynaecology, Society of Obstetricians and Gynaecologists (Johnston & Farrell, 2004). Overall, the recommendations alert the practitioner to routinely evaluate post-menopausal women for vaginal atrophy. The guideline also recommends use of local hormone replacement, an estrogen cream, the estradiol-containing vaginal ring, or estradiol-containing tablets for women with symptoms of vaginal atrophy or those having recurrent UTIs. The guideline does not recommend annual surveillance for endometrial proliferation because of insufficient data (Johnston & Farrell, 2004).

Assessment of vaginal atrophy in post-menopausal women is not always clear cut. In clinical practice, it may be necessary to phrase the question in more than one way to detect if there is a problem. Asking about the frequency of dysuria, painful intercourse, or UI may not be revealing. But asking if the patient has itching or burning in the vaginal area after intercourse or if she needs to use a vaginal lubricant-containing vaginal ring may be more useful. The guideline recommends using the clinician to identify physiological changes during pelvic examination and gently broach the subject. Variable results continue to be reported on the use of vaginal estrogen on the treatment of UI.

As clinicians, we think in terms of prevention and health maintenance. This is yet another area for urologic health care providers to be aware when involved with women’s health care. Preventing vaginal atrophy with the onset of menopause can minimize discomfort and UTIs. Although the studies are not conclusive, there is evidence to indicate the use of topical estrogen may have a role in preventing recurrent UTIs and relieve symptoms of vaginal atrophy associated with menopause or the decrease in estrogen in vaginal tissues. It must be stressed, however, that all hormone therapy, whether systemic or local, should be considered carefully by the clinician in rela-
tionship to the patient’s clinical presentation and risk profile.

References


