

## Chronic Unopposed Vaginal Estrogen Therapy

The question of whether progestagen opposition is required in a patient on chronic vaginal estrogen is controversial. The literature is not clear on this matter and the SOGC conference on Menopause did not reach a consensus.

Endometrial hyperplasia is directly related to the dose and duration of estrogen therapy. **The PEPI study showed that 10 per cent of women taking unopposed estrogen (equivalent to 0.625 mg CEE) will develop complex or atypical endometrial hyperplasia within 1 year.** With long-term HRT, it is now considered standard practice to add progestagen opposition to *oral* estrogen therapy in women with an intact uterus. The case is less clear for vaginal estrogen therapy. The makers of Premarin® vaginal cream indicate their product is for short term management of urogenital symptoms and the monograph clearly states "precautions recommended with oral estrogen administration should also be observed with this route".

In one recent study looking at "Serum and tissue hormone levels of vaginally and orally administered estradiol" (Am J Obstet Gynecol 1999;180:1480-3), serum levels were 10 times higher after vaginal vs. oral administration for exactly the same dose while endometrial concentrations were 70 times higher. This suggests that in some cases very little estrogen is required vaginally to produce significant serum levels and there may be preferential absorption into the endometrium. Hence equivalent vaginal doses may sometimes be much lower on a mg per mg basis compared to oral, largely because of bypassing the "first pass" effect. When equivalent doses are administered vaginally, serum levels are about 25 per cent of those seen with oral doses (SOGC Consensus 1998). In some studies, oral doses of 0.3 mg conjugated estrogens (equivalent to 0.5gm or 1/8 applicator of Premarin®) did not produce changes in serum estrogen levels; however, in some cases it may still be sufficient to cause endometrial hyperplasia (SOGC Consensus 1998). Handa et al looked at "Vaginal administration of low-dose conjugated estrogens; systemic absorption and effects on the endometrium" (Obstet Gynecol 1994; 84: 215-18). In 20 women receiving 0.3mg pv 3 times weekly for 6 months, atrophic vaginitis was relieved with minimal endometrial hyperplasia. These results must be interpreted cautiously given the small number of subjects and relatively short duration of treatment.

Any bleeding during treatment should be followed up to rule out malignancy. Although the risk of endometrial hyperplasia/carcinoma is probably much lower than with oral therapy, patients should be monitored in the same manner as any woman receiving unopposed estrogen. In this case the SOGC Consensus advocates yearly endometrial biopsy; if biopsy is unacceptable or not possible, assessment of the endometrium can be done by transvaginal ultrasound (TVU) - a thickened endometrium (>5mm) warrants further evaluation. A technical bulletin from the American College of Obstetricians and Gynecologists (HRT #166, 1992) suggests the use of a progesterone challenge test (PCT) - if no vaginal bleeding occurs after giving medroxyprogesterone (Provera®) 10 mg po OD x 10-13days the patient is considered to be at low risk and the PCT and TVU can be repeated periodically (annually) to evaluate status of the endometrium. If bleeding occurs in response to the PCT, the vaginal estrogen therapy should be combined with either continuous or periodic progestagen (presumably in similar fashion to oral regimens).

Depending on the case, one may also consider a change to a non-estrogen vaginal moisturizer such as **Replens®** which is clinically effective in treating menopausal urogenital symptoms. Alternately, **Estring®** could be substituted for the Premarin® cream; serum estradiol levels are undetectable 48 hrs after insertion of the ring. In a U.S. study, endometrial overstimulation evaluated by progesterone challenge test and pelvic sonogram was reported in 0 of 58 non-hysterectomized women using Estring® as compared to 4 of 35 patients using vaginal cream (Estring® product monograph). While this does not preclude the risk of endometrial hyperplasia completely (remember the possibility of preferential uptake by the endometrium), it is much less likely to occur with this product. Estring® is comparable in cost to therapy with topical patches (~ \$320/year).

**In Summary:** there are no clear guidelines regarding the need for progestagen opposition in patients on chronic vaginal estrogen. Given that vaginal estrogen is systemically absorbed and that endometrial levels may be significantly higher than systemic levels, some precautions should be taken with chronic therapy unless the patient is on very low doses (e.g. 1/4 applicator Premarin® once weekly). Precautions may include using progestagen opposition, or increased monitoring for potential endometrial hypertrophy and cancer. Alternately, Replens® vaginal moisturizer or Estring® may be potentially safer alternatives in select patients.