November 2006 · Vol. 18, No. 11
EXAMINING THE EVIDENCE
CLINICAL IMPLICATIONS OF KEY TRIALS

Q

Which works better: Vaginal or oral estrogen for atrophy and dyspareunia?

Long C-Y, Liu C-M, Hsu S-C, et al. A randomized comparative study of the effects of oral and topical estrogen therapy on the vaginal vascularization and sexual function in hysterectomized postmenopausal women. Menopause. 2006;13:737-743.

Anthony A. Luciano, MD
Director of the Center for Fertility and Women's Health, and Director of Endoscopic Surgery, Center for Advanced Reproductive Services, and Professor of Obstetrics and Gynecology, University of Connecticut School of Medicine, New Britain, Conn

FAST TRACK

Systemic absorption of vaginal estrogen is greater and more rapid than oral estrogen

A

Vaginal estrogen administration led to greater improvement of both dyspareunia and vaginal dryness in postmenopausal hysterectomized women—despite higher serum estradiol levels with the oral route. Vaginal estrogen had no effect on libido, whereas oral estrogen may lower libido because of related increases in sex hormone binding globulin (SHBG), which decreases free testosterone levels.

Expert Commentary

METHODS Investigators randomized 57 postmenopausal, hysterectomized women to receive oral (0.625 mg of conjugated equine estrogen [CEE]; n=27) or vaginal (0.625 mg of CEE per 1 g of vaginal cream; n=30) estrogen once daily.

Vaginal vascularization and sexual function were assessed through a variety of measures, including serum estradiol, introital color Doppler ultrasound, and personal interviews.

RESULTS After 3 months of treatment, both groups of women had significant increases in the number of vaginal vessels, and "marked" decreases in the pulsatility index.

- **Anorgasmia** decreased significantly in both groups.
- **Sexual function in the vaginal dryness and dyspareunia** domains was significantly improved with vaginal estrogen therapy, but not with oral

administration. However, the efficacy of oral therapy for vaginal dryness and dyspareunia was 80% and 70.6%, respectively. For vaginal therapy, the corresponding figures were 79.2% and 75%, respectively.

Unopposed estrogen has its own benefits, risks

In hysterectomized postmenopausal women, unopposed estrogen has been shown to relieve menopausal symptoms and protect against bone loss and osteoporosis-related fractures without increasing the risk of breast cancer or cardiovascular disease.

- **Oral** estrogen increases the risk of stroke and venous thromboembolic events (VTE), and may decrease libido, as mentioned above.
- **Transdermal** administration has not been associated with decreased libido, and may be associated with a lower risk of VTE.[1,2]

Don't be fooled by serum levels

Measurements of serum estradiol levels in women who are taking CEE either orally or vaginally do not truly reflect the total estrogenic load of these patients, because the bulk of estrogen in CEE is estrone sulfate with several equine estrogenic compounds that have activity not reflected by serum estradiol. Consequently, the estrogenicity of the women in this study was not accurately evaluated through the serum estradiol measurements.

Vaginal estrogen is *not* "topical"

Moreover, the authors refer to the vaginal group as receiving "topical" estrogen—another misconception. Systemic absorption of vaginal estrogen is probably greater and more rapid than with the oral route. It is no surprise that vaginal administration was associated with greater improvement of both dyspareunia and vaginal dryness, because the vagina is exposed to a greater concentration of estrogen when it is administered vaginally than when it is given orally. With oral administration, a significant amount of estrogen is metabolized by the liver, and a much lower dose of estrogen reaches the vaginal epithelium.

Oral estrogen can reduce libido

The lack of improved libido with the oral preparation is not surprising. In fact, some women may experience a decrease in libido with orally administered estrogen because of the associated increases in SHBG. With vaginal administration, SHBG levels are not increased, and sexual desire may improve, especially when vaginal lubrication is improved.

Does either form affect sexual function? Unfortunately, this study was not long enough or sufficiently powered to adequately assess sexual function.

Systemic absorption is high even with vaginal route

The same dose of CEE yields slightly greater benefits to vaginal health and function when it is administered vaginally. When estrogen is given vaginally, systemic absorption is significant—and may be greater than with the oral route.

Indications and contraindications of oral estrogen, consequently, also apply to vaginal administration.

R E F E R E N C E S

1. Scarabin PY, Oger E, Plu-Bureau G. For the Estrogen and Thromboembolism Risk Study Group. Differential association of oral and transdermal oestrogen-replacement therapy with venous thromboembolism risk. Lancet. 2003;362:428–432.
2. Straczek C, Oger E, Yon de Jonage-Canonico MB, et al. For the Estrogen and Thromboembolism Risk Study Group. Prothrombotic mutations, hormone therapy, and venous thromboembolism among postmenopausal women: impact of the route of estrogen administration. Circulation. 2005;112:3495–3500.