

# NEWS

## Commentary

The following news items are reviews of important scientific articles with commentary that address clinical relevance. This material comes from the First to Know® monthly e-newsletter published by The North American Menopause Society (NAMS), offered to its members via broadcast e-mail. You can receive a subscription by joining the Society ([www.menopause.org](http://www.menopause.org)). Please note that the opinions expressed in the commentaries are those of the authors and are not necessarily endorsed by NAMS.

### ET/EPT linked to increased risk of urinary incontinence symptoms

Hendrix SL, Cochrane BB, Nygaard IE, et al. Effects of estrogen with and without progestin on urinary incontinence. *JAMA* 2005;293:935-48.

Postmenopausal estrogen therapy, either with or without a progestin, increases the risk of urinary incontinence (UI) in continent women and worsens UI symptoms in incontinent women, according to this analysis of data from the Women's Health Initiative (WHI), a randomized, placebo-controlled, double-blind, multicenter clinical trial. Participants were postmenopausal women aged 50 to 79 years for whom UI symptoms were known. Women received either placebo or conjugated equine estrogens (CEE) at 0.625 mg/day (plus medroxyprogesterone acetate at 2.5 mg/day for women with a uterus). Urinary symptoms were recorded for 23,296 women at baseline and after 1 year of hormone therapy, using a self-administered behavioral and quality of life form.

Estrogen-containing therapy significantly increased the incidence of UI—

stress, urge, and mixed—at 1 year among women who were continent at baseline. The relative risks (RRs) for stress incontinence were 2.15 (95% CI, 1.77-2.62) for estrogen alone (ET) and 1.87 (95% CI, 1.61-2.18) for estrogen plus progestin (EPT). The risk of developing urge UI was significantly increased by ET (RR, 1.32; 95% CI, 1.10-1.58) but not by EPT (RR, 1.15; 95% CI, 0.99-1.34). The RRs for mixed UI were 1.79 (95% CI, 1.26-2.53) for ET and 1.49 (95% CI, 1.10-2.01) for EPT.

Among women with UI at baseline, both ET and EPT significantly worsened symptoms. Frequency risk increased by 47% in ET users (95% CI, 1.35-1.61) and 38% in EPT users (95% CI, 1.28-1.49). Amount of UI leakage worsened by 59% with ET (RR, 1.59; 95% CI, 1.39-1.82) and 20% with EPT (RR, 1.20; 95% CI, 1.06-1.36).

Women receiving ET/EPT were significantly more likely to have UI symptoms that limited their activities of daily living or were bothersome. For ET, the RRs were 1.29 (95% CI, 1.15-1.45) and 1.50 (95% CI, 1.37-1.65), respectively. For EPT, the RRs were 1.18 (95% CI, 1.06-1.32) and 1.22 (95% CI, 1.13-1.32).

**Comment.** Whether estrogen should be used to treat UI is controversial. Both alpha and beta estrogen receptors are present in the urogenital tract, and physiologic studies have suggested that estrogen has a positive effect. A Cochrane Review [Moehrer *Cochrane Database Syst Rev* 2003] concluded that estrogen is an effective treatment for UI. However, the randomized, controlled trials included in that systematic review all showed that estrogen treatment had a negative or neutral effect on UI in postmenopausal women.

This secondary analysis of the WHI by Hendrix and colleagues provides the best and most detailed information about the effects of oral CEE on UI symptoms in postmenopausal women. The study confirms findings from the Heart and

Estrogen/progestin Replacement Study (HERS) [Brown *Obstet Gynecol* 1999] that EPT worsens stress, urge, and mixed UI symptoms.

It also provides important novel information. First, CEE alone worsened all types of UI. Second, CEE alone increased the risk of developing all types of UI, and EPT increased the risk of both new-onset stress and mixed UI. Additionally, an analysis of secondary outcomes showed that leakage amount, bothersome symptoms, and impact on quality of life all increased with CEE use, emphasizing the clinical importance of the study's conclusions.

As the authors note, it is not known whether the results seen with CEE (with or without medroxyprogesterone) at a standard oral dose can be generalized to all estrogens. However, the quality of this study provides a high level of evidence to recommend against the use of estrogen for the prevention and treatment of UI in postmenopausal women, at least until different types and routes of estrogens can be as rigorously investigated.

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**Comment.** The WHI was not designed to evaluate the risks of UI, and it certainly wasn't designed to determine causality. However, the fact that stress incontinence increased more than urge incontinence might lead to the assumption that an increase in uterine volume was the cause. This could be substantiated by data from the Nurses' Health Study [Grodstein *Obstet Gynecol* 2004], showing ET/EPT increased UI but that the UI was totally diminished by cessation of hormone use. Other studies, although much smaller, have actually reported improvements with ET/EPT. Even in

the HERS report of overall risk of UI with EPT, [Grady *Obstet Gynecol* 2001] 20% of EPT recipients reported improvement in UI.

What does this mean clinically? It would be very rare to treat any UI with estrogen as a first-line therapy (unless clearly from atrophic urethritis). However, it would be important to know if, while treating other symptoms, the possibility of UI is a concern.

In the WHI study, UI was determined by self-report. Information regarding medical history and/or surgical treatment was not collected. Therefore, it is not possible to know how many women in each group sought medical care, or to ascertain the true impact of symptoms. However, women in the 50-to-54 age group did not show any significant association between UI and hormone use, and this age group represents the majority of women using ET/EPT. In addition, the actual number of women with quality of life impact seems to be small, and other studies have not found this association. When coupled with the Nurses' Health Study results showing total reversibility of estrogen-associated UT, it makes this UI increase important information to know and share. However, it should not be a significant concern if hormone therapy is indicated.

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## Hormone levels differentiate menopause-transition stages

Freeman EW, Sammel MD, Gracia CR, et al. Follicular phase hormone levels and menstrual bleeding status in the approach to menopause. *Fertil Steril* 2005;83:383-92.

Serum levels of estradiol, follicle-stimulating hormone (FSH), luteinizing hormone (LH), and inhibin B are significantly associated with different stages of the menopausal transition, according to this

prospective, longitudinal study. A random sample of 436 community-dwelling women aged 35 to 47 and with regular menstrual cycles at enrollment were followed for 5 years. Data were collected in the early follicular phase of two consecutive menstrual cycles for estradiol, FSH, LH, and inhibin B along with menstrual cycle information at seven assessment points, ranging from 8-month to 1-year intervals.

Menstrual cycle status was used to define five menopause-transition stages: premenopause (baseline), late premenopause, early transition, late transition, and postmenopause. Levels for all four measured hormones differed significantly from the premenopause to postmenopause stages ( $P < 0.001$ ). Both FSH and LH reached significantly higher levels at the early transition stage. Inhibin B levels reached significantly lower levels starting with the late premenopause stage. Estradiol levels were relatively stable until the postmenopause stage, at which point they were significantly lower.

Race, menstrual status, and body mass index (BMI) all were significantly associated with hormone levels. Women with a BMI greater than 30 had significantly higher levels of estradiol, LH, and inhibin B than did those with lower levels. African-American women had significantly lower levels of estradiol and LH than did Caucasian women (the only two races compared) during the premenopause stages. In postmenopausal women, African-Americans with high BMI levels had the highest estradiol levels.

**Comment.** The data in this report essentially confirm results from a number of studies, both cross-sectional and longitudinal, demonstrating that changes in cycle regularity as menopause approaches are accompanied by, and presumably somehow reflect, changes in reproductive hormones, especially inhibin B and FSH. In this report, women in late premenopause who had only a single menstrual cycle, the length of which was 7 or more days different from their previous pattern, had a

highly statistically significant decline in inhibin B and a significant, though small, increase in FSH.

The authors adapted the reproductive aging definitions from the Stages of Reproductive Aging Workshop (STRAW) by including the late premenopause stage, by specifying the definition of early transition on the basis of at least two such cycles, and using a 3- to 11-month period of amenorrhea (rather than 60 days) as the basis for the late transition. As has been pointed out elsewhere, the STRAW criteria for the early transition are somewhat ambiguous with regard to the occurrence of cycle irregularity or of cycle regularity but at an altered frequency.

Disappointingly, there is no analysis of changes in hormone levels in the 47% of women who remained premenopausal during the 5-year study. This would have been of interest given the recent report by Landgren et al [7 *Clin Endocrinol Metab* 2004] demonstrating that at least two types of cycles can be observed in women as they approach menopause: ovulatory cycles showing no change in follicular phase hormone levels over time, and apparently anovulatory cycles characterized by elevated FSH and LH levels and elevated ratios of FSH to either inhibin A or inhibin B. This illustrates the limitations imposed by a sampling schedule confined to the follicular phase. It is also unclear as to how data from women whose menopausal status changed during the study were incorporated into the analysis.

Geometric mean levels for estradiol were lower only in postmenopausal women. Levels of FSH rose mainly in the late transition, as did LH, while inhibin B fell progressively throughout the study. These data confirm a report [Burger *Clin Endocrinol (Oxf)* 1998] that the earliest hormonal change of significance in the early transition was the fall in inhibin B. As Freeman et al observed, "these early hormonal changes are unlikely to be detected with single hormone measures in clinical practice." However, a self-report of the

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