

POST MENOPAUSAL HORMONE THERAPY TODAY

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INTRODUCTION

Menopause is an important passage for all women, whether they view it as a welcome end to fertility and menstrual cycles or as an unwanted symbol of aging. Of the many negative symptoms associated with menopause, only vasomotor symptoms (hot flushes and night sweats) and urogenital atrophy are attributed directly to the decline in ovarian function. Other changes attributed to menopause may be related to aging itself or to psychosocial pressures that women at midlife experience, but some are likely logical sequelae to genuine menopausal symptoms: clearly, vasomotor symptoms disrupt sleep, and sleep-deprived people can become moody and forgetful; vaginal atrophy makes intercourse painful, which, without intervention, can result in diminished interest in sexual activity. Appropriate attention to menopausal symptoms can assist multiple areas of a patient's well-being and quality of life.

CLINICAL CHANGES

Distinct hormonal and physical changes mark the entry into menopause. Although studies suggest that hormonal changes begin to occur in women in their 30s and early 40s prior to the onset of menstrual irregularities that traditionally define perimenopause, little is known about possible clinical manifestations of decreased ovarian function in this age group. Multiple studies support that the menopause transition occurs for most women between 45 and 55 years of age and is associated with a number of symptoms that affect quality of life. Among these are hot flushes, disrupted

sleep, and vaginal atrophy.¹ The Massachusetts Women's Health Study, a comprehensive survey of 2,750 Caucasian women aged 45 to 55 years, estimates that the length of the perimenopausal transition is approximately four years with >46% of patients reporting symptoms.²

As a woman transitions to menopause, symptoms associated with estrogen loss are prominent even in women who are still regularly cycling. However, symptoms have been documented to occur more frequently or more intensely as menses become more irregular. In the SWAN (Study of Women's Health Across the Nation) cohort, a community-based, multiracial/multiethnic sample of 16,065 women aged 40 to 55 years, the largest adjusted prevalence odds ratio for all symptoms, particularly hot flushes or night sweats (OR=2.06–4.32) was for women who were peri- or postmenopausal.³ In a 12-year longitudinal study of 160 healthy 48-year-old women, Rannevik identified decreases in both estradiol and estrone during the 6-month period around the menopause⁴ (Figure 1). Following menopause, both estrogens continued to decline. The physiological symptoms that have been reported to occur during this transition are significant in number and have been found to increase in prevalence and frequency within six to 12 months before and after the last menstrual period. In this study, the severity of symptoms such as trouble sleeping, vaginal dryness, night sweats, and hot flushes were all increased in late perimenopause and postmenopause as compared to the earlier perimenopausal years. Prevalence and frequency of these symptoms have been shown to be affected by lifestyle,

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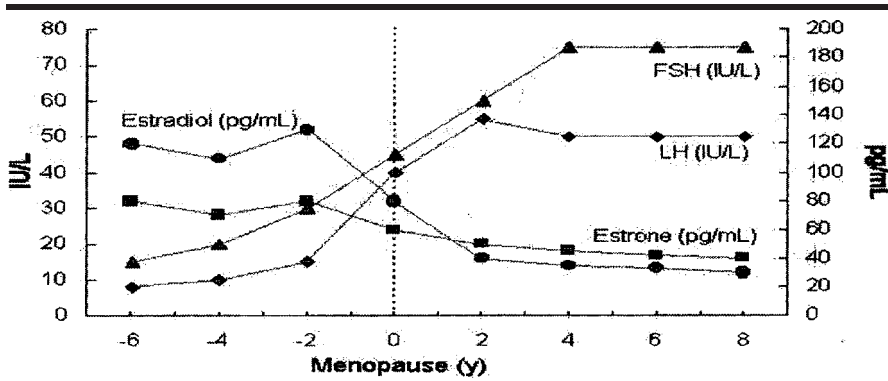


Fig 1. Ovarian and pituitary hormone serum levels during the menopause transition. FSH=follicle-stimulating hormone; LH=luteinizing hormone
Adapted from Rannevik G, Jeppsson S, Johnell O, Bjerre B, Laruell-Borulf Y, Svanberg L. *Maturitas*. 1995;21:103-113.

menstrual status, race, and ethnicity.^{3(p466)}

VASOMOTOR SYMPTOMS

The relationship between declining serum levels of estrogen and vasomotor symptoms has been documented. Symptoms associated with vasomotor instability include hot flashes, night sweats, dizziness, headaches, palpitations, and insomnia. The greatest change in the severity of the symptoms has been documented to occur during the phase of

maximum changes in levels of follicle stimulating hormone and estradiol levels. In a longitudinal population-based study, which included measurement of hormone levels, the development of hot flashes in late menopause was more increased for middle levels of estradiol (30-100 pmol/L) as compared to lower levels of estradiol (<30 pmol/L), suggesting that hot flashes are precipitated by falling levels of estradiol^{1(p357)} (Figure 2). Although the exact etiology of hot flashes remains unclear, based on the instability in the hypothalamic thermoregulatory center that occurs in response to

estrogen withdrawal, it is considered to be a hypothalamic mechanism.

Estrogen therapy in multiple dose levels has been shown to be effective in reducing both perceived and objectively measured occurrences of hot flashes in postmenopausal women. In a 12-week study that examined the effects of oral 17 β-estradiol (0.25 to 2.0 mg) for the relief of vasomotor symptoms in 333 menopausal women, at 4 weeks 17 β-estradiol therapy significantly decreased the number and the severity of hot flashes compared with placebo (P<.001).⁵ Investigators in the PEPI (Postmenopausal Estrogen/Progestin Interventions) trial assigned 875 women (mean age, 56 years) to one of four active therapies (each of which included conjugated equine estrogens [CEE] at a dose of 0.625 mg/day either alone or in combination with a progestin) or to placebo. The CEE was shown to significantly reduce hot flashes as compared to placebo.⁶

Transdermal estrogen therapy is similarly effective.⁷ In a study of 1,465 postmenopausal women with greater than one vasomotor symptom per day, 25 μg 17 β-estradiol patch reduced the mean number of hot flashes by 93% at month 4 and overall was reported to be better tolerated than the 50 μg patch.⁸

The 2-year Women's HOPE (Health, Osteoporosis, Progestin, Estrogen) study evaluated the efficacy and safety of lower doses of CEE alone and continuously combined with different MPA doses in healthy postmenopausal women at 57 centers across the United States. This prospective, randomized, double-blind, placebo-controlled, multicenter trial included 2,673 women aged 40 to 65 years, who were randomized to receive one of eight treatment regimens (in mg/day):

- CEE 0.625
- CEE 0.625/MPA 2.5
- CEE 0.45
- CEE 0.45 /MPA 2.5
- CEE 0.45/MPA 1.5
- CEE 0.3

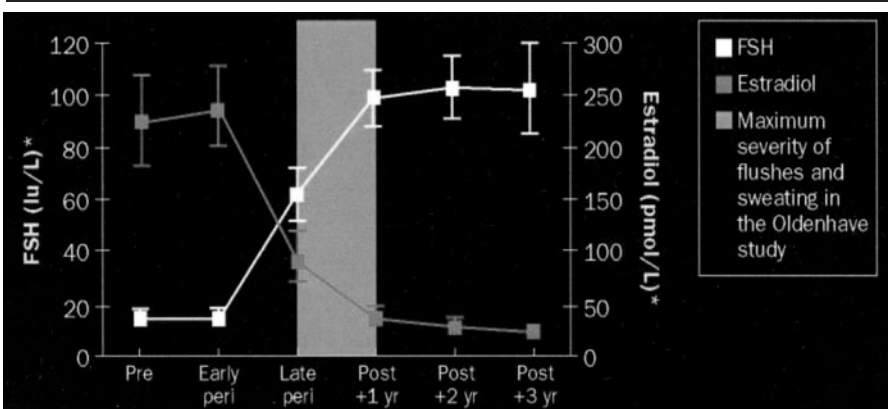


Fig 2. Hormonal changes from premenopause to postmenopause.
*Geometric means of hormone levels; 172 women, ages 45-55 years; 7 years followup.
Adapted from Dennerstein et al. *Obstet Gynecol*. 2000;96:351 and Oldenhave et al. *Am J Obstet Gynecol*. 1993;168:772.

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- CEE 0.3/MPA 1.5
- Placebo

The study design included a focus on menopausal symptoms, endometrial histology, and bleeding profiles for 13 cycles (year 1), and a substudy that focused on bone density and turnover, serum lipoproteins, and carbohydrate metabolism (year 2). In the Women's HOPE study, the reported number and severity of hot flushes was significantly reduced from baseline for all active treatment groups, when compared with placebo. Lower doses of CEE alone (0.45 mg/day and 0.3 mg/day) were effective in decreasing the number and severity of hot flushes, but were not as effective as CEE at 0.625 mg/day. However, all lower doses of CEE combined with MPA were similar to CEE 0.625 mg/MPA 2.5 mg for relief of vasomotor symptoms.⁹

Vasomotor symptoms have a considerable impact on a woman's quality of life. Aside from recommendation from a clinician, symptoms are the most common reason for beginning HT or ET during the menopausal transition.¹⁰

UROGENITAL ATROPHY

Vulvovaginal and urogenital atrophy are manifestations of estrogen deprivation. This most commonly occurs following menopause, however, any medical or surgical condition during the premenopausal years which results in decreased estrogen levels may predispose a woman to these conditions. Urogenital problems are reported to affect as many as 40% of postmenopausal women and 15% of premenopausal women.¹¹ Patients may present with a variety of symptoms that reflect the abundance of estrogen receptors in the vaginal epithelium, bladder, and urethra (Figure 3). The prevalence of vaginal dryness was reported to be 13.1% for women participating in the SWAN survey, with significant differences noted based on race and ethnicity. As compared to Cauca-

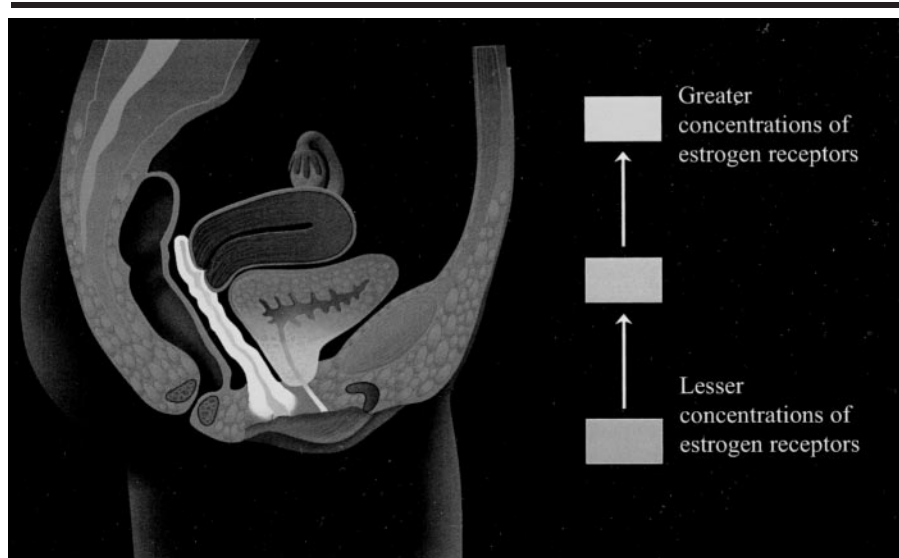


Fig 3. Estrogen receptor concentrations in select adult female tissues.
Adapted from Blackeman PJ et al. *BJU International*. 2000;86:32-38.

sian women in this survey, African-American and Hispanic women reported the highest rates of vaginal dryness and urinary leakage.^{3(p466)} In a Swedish study of more than 4,500 women aged 46 to 62, vaginal dryness was reported to occur increasingly as women aged, so that the prevalence among the 62-year-old women reached 34%.¹² In a study

conducted by Bachmann and coworkers, dyspareunia was reported by 30% of postmenopausal women not taking hormone therapy; women reporting little or no coital activity also had been documented to have a lower vaginal atrophy index score (indicative of more vaginal atrophy)¹³ (Figure 4).

The effectiveness of estrogens in re-

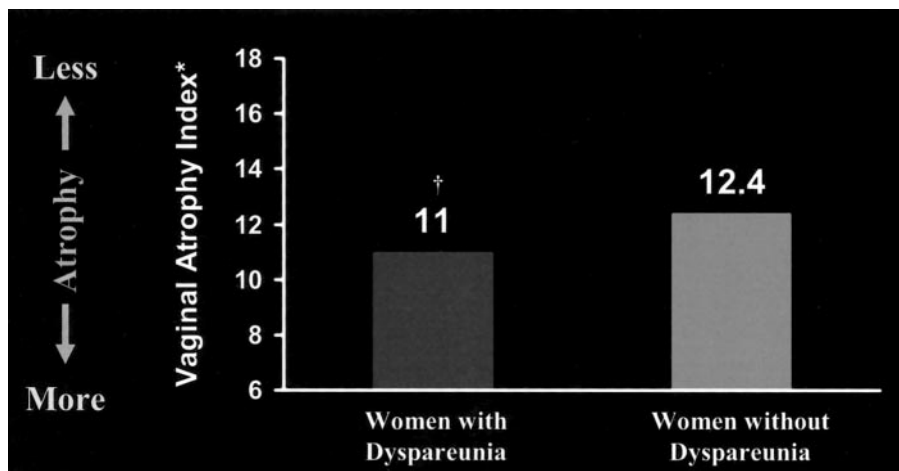


Fig 4. Effect of vaginal atrophy

*Vaginal atrophy index derived from evaluation of skin elasticity and turgor, pubic hair, labia, introitis, and vaginal mucosa and depth. The lower the score, the more atrophy present.

† $P = .02$ vs women without dyspareunia

Adapted from Bachmann et al. *Fem Patient*. 1984;9:118-127.

storing the normal vaginal epithelium has been well established. Estrogen quickly restored the vaginal pH to a healthy premenopausal level within one month of receiving CEE, 1.25 mg/day. In this study, sexual activity and HT were associated with a more normal pH.¹⁴ Lower doses of CEE and CEE/MPA were also effective in improving the Vaginal Maturation Index, an assessment of vaginal atrophy. The percentage of vaginal superficial cells was significantly improved from baseline following treatment with either systemic CEE alone or combined with MPA.^{9(p1072)}

SEXUAL CHANGES

According to the National Health and Social Life Survey, a survey of men and women between the ages of 18 and 59, 43% of women in the United States experience some type of sexual dysfunction.¹⁵ Changes in sexual function occur in many women during the immediate postmenopausal years, secondary to diminished sexual response and vaginal dryness.^{13(p27)} Declines in sexual activity and lack of an available partner also occur. The degree of distress experienced by women who note postmenopausal changes in their sexual lives reflects their premenopausal interest in sex.¹⁶ Several studies have shown that estrogen levels are a significant factor in genital health, vaginal lubrication, and complaints of dyspareunia¹⁷ (Figure 4). In a study by Nathorst-Boss et al, 12 weeks of transdermal ET improved satisfaction with frequency of sexual activity and sexual fantasies in postmenopausal women between the ages of 45 and 65.¹⁸

URINARY IMPLICATIONS

With menopause, the lower urinary tract epithelium, like the vagina, undergoes atrophic changes secondary to estrogen loss. Vaginal atrophy can bring the urethral opening in closer proximity to vaginal introitus, increasing the risk

of contamination of the vaginal flora to the urethra and contributing to urinary tract infections (UTIs). Urethral closure pressure also decreases with urethral atrophy, increasing the likelihood of urethral irritation and incontinence. Intra-vaginal estriol cream and estradiol-releasing vaginal rings have both been shown to be effective in preventing recurrent UTIs.^{19,20}

Estrogen loss also leads to changes in the strength of the connective tissues and muscles supporting the urethra, bladder, and rectum. Laxity of the ligaments supporting the pelvic viscera leads to prolapse and other disorders that also contribute to incontinence. Among community-dwelling older adults, 15% to 30% are believed to experience urinary incontinence, with rates twice as high in women as in men. Of these patients, only about half have consulted a doctor about the problem.²¹

The majority of patients who present with urinary incontinence have a combination of detrusor instability (a form of urge incontinence) and genuine stress incontinence. A meta-analysis of 23 studies evaluating the efficacy of estrogen supplementation in the management of postmenopausal women with urinary incontinence, from the First Report of the Hormones and Urogenital Therapy Committee, reported a significant improvement on subjective symptomatology for all patients receiving estrogen therapy.²²

The decline in estrogen levels after menopause is associated with urogenital atrophy and sexual changes, and can be treated with estrogen (or estrogen plus progestin therapy, as appropriate). However clinicians must be proactive in directing discussion with patients to determine if these problems exist and, if so, explain the role of estrogen in sexuality and overall urogenital health.

MENOPAUSAL SYMPTOM MANAGEMENT POST-WHI

Helping patients identify individual goals and objectives as they relate to

menopausal issues is the most important aspect in the decision to consider hormone therapy. While the Women's Health Initiative (WHI) trial provides healthcare providers with much-needed prospective data on the risks and benefits of HT, media coverage of the premature end of the estrogen plus progestin arm in July 2002 left many patients confused, upset, and questioning whether they should continue or ever initiate therapy. Deciding whether to begin or continue HT should be based upon the symptoms and health risks presented by the patient, weighed in light of objective scientific data.

In order to adequately address patient concerns, we must provide information that is both culturally sensitive and clinically relevant to them. Domm and coworkers surveyed 114 women to determine their level of knowledge and sources of information about menopause. They revealed a significant dichotomy according to level of formal education and race. Among women with a high school-only education, 46.7% of Caucasian women but 0% of African-American women reported having access to menopause information.²³ However, among women with a college education or greater, 55.6% of African-American women had access to menopause information. Of the women who did have access to information, 91% rated themselves as "very" or "somewhat" knowledgeable about menopause. Women's accounts of their menopausal experiences also differ according to socioeconomic status.^{3(p470)} Clearly, information must be presented at an appropriate comprehension level. Once the patient is informed, concerns must be addressed, taking into consideration the multitude of issues such as race, family history, and the type, dose and length of hormone therapy. Then the physician can review the various appropriate treatment options with the patient so they can reach a decision together. This level of counseling and decision-making must be revisited at least annually, and poten-

tially more often if new information emerges or the woman's circumstances changes.

For the symptomatic patient, HT adherence will depend upon her belief that the benefits of therapy outweigh the risk. A well-informed patient who understands at the onset what side effects may occur and that she may have other therapeutic options will be less likely to discontinue therapy at the first sign of unwanted effects. Rather, she may be more likely to report any side effects and look to the physician for guidance on management.

QUALITY OF LIFE

Quality of life (QOL) commonly is defined as general health assessments that allow comparisons of healthcare interventions across multiple disease areas. For the menopausal woman we typically assess vasomotor symptoms, anxiety, somatic complaints, depressive symptoms, and sexuality before and after a therapeutic intervention. Oldenhav and coworkers evaluated 5,213 women aged 39 to 60 years of age to assess the impact of menopause on well-being. As many as 85% of the patients reported having hot flushes by late premenopause to early postmenopause. Patients also reported a multitude of nonvasomotor complaints that they perceived to increase in frequency with the severity of the hot flush²⁴ (Figure 5).

Derman and coworkers randomized women who complained of vasomotor symptoms to sequential 17-beta estradiol plus norethindrone acetate or placebo. In addition to assessing change in frequency and intensity of vasomotor symptoms, the investigators evaluated QOL measures pre- and post-treatment using the Kupperman Index, Greene Index, and the Beck Depression Inventory. Statistically significant QOL improvements were noted in concert with improvement in vasomotor symptoms among the treatment group.²⁵ Earlier,

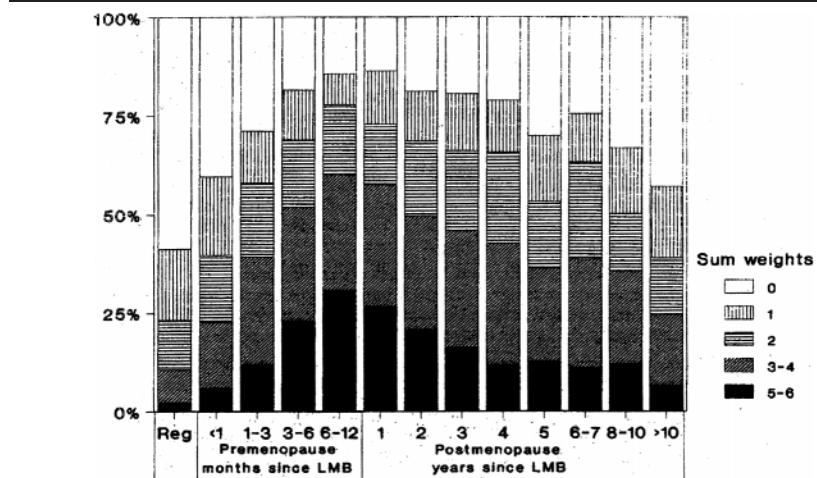


Fig 5. Impact of climacteric on well-being. Severity of vasomotor complaints according to climacteric status in 5213 women aged 39 to 60 years. LMB=last menstrual bleeding; Reg=regular menstrual pattern. Adapted from Oldenhav A. et al. *Am J Obstet Gynecol.* 1993;168:772.

Wiklund and coworkers had assessed several different areas of QOL using four different scales in patients before and after 3 months of transdermal estradiol. For all measures assessed, patients experienced QOL improvements, but the improvement was greater among treated patients.²⁶ Finally, in an assessment of health-related QOL according to HT use, Tosteson reported that current users of HT rated their vitality, role function (physical, emotional), and mental health higher than past or never users did.²⁷

The PEPI investigators found that patients assigned to active treatment (CEE alone or with progestin) had significantly fewer vasomotor symptoms but did not differ from patients taking placebo in levels of anxiety, cognitive, or affective symptoms.^{6(p985)} In the HERS trial, postmenopausal women younger than 80 years with documented coronary artery disease (mean age, 67 years) completed QOL questionnaires. An association was found between flushing symptoms and the impact of hormone therapy, with generally positive effects of hormone therapy on quality of life among women with flushing and generally negative effects among women without menopausal symptoms.²⁸ Al-

though QOL was not an endpoint of the WHI hormone study, investigators did collect QOL data, and found that combined HT was associated with a slight benefit on sleep disturbance but no benefit in other QOL outcomes.²⁹ It should be noted that women troubled with vasomotor symptoms (who, according to the HERS findings, would be most likely to experience QOL benefits from HT) were unlikely to enroll in WHI if they were unwilling to risk assignment to the placebo group.

CONCLUSION

In response to publication of the WHI and HERS reports, The North American Menopause Society (NAMS) convened an advisory panel to develop recommendations for using HT in clinical practice. Among its conclusions:

- younger, symptomatic women were not represented in either study, and so results cannot necessarily be extrapolated to that population;
- HT should be prescribed primarily for relief of menopausal symptoms such as vasomotor and urogenital effects,

and it should be weighed against other options for osteoporosis prevention;

- HT should be used at the lowest effective dose for the shortest time required to achieve treatment goals, and;
- the decision to use HT should rest with the patient, once she has been notified of the risks and benefits as they apply to her.³⁰

Quality of life may be severely affected by vasomotor symptoms, since they can be disruptive, physically debilitating, and embarrassing. Studies have shown that HT, by alleviating hot flushes and related symptoms such as sleep disruption, enhances quality of life for the symptomatic patient.^{25(p40),31} The decision to begin or continue HT is an individualized and personal choice, but clearly should include evidence-based data that considers a patient's need for symptom relief as part of the risk/benefit equation.

REFERENCES

1. Dennerstein I, Dudley EC, Hopper JL, et al. A prospective population-based study of menopausal symptoms. *Obstet Gynecol.* 2000;96:351-358.
2. McKinlay SM, Brambilla DJ, Posner JG. The normal menopausal transition. *Maturitas.* 1992;14:103-115.
3. Gold EB, Sternfeld B, Kelsey JL, et al. Relation of demographic and lifestyle factors to symptoms in a multi-racial/ethnic population of women 40-55 years of age. *Am J Epidemiol.* 2000;152:463-473.
4. Rannevik G, Jeppsson S, Johnell O, et al. A longitudinal study of the perimenopausal transition: altered profiles of steroid and pituitary hormones, SHBG, and bone mineral density. *Maturitas.* 1995;21:103-113.
5. Notelovitz M, Lenihan JP, McDermott M, et al. Initial 17 beta-estradiol dose for treating vasomotor symptoms. *Obstet Gynecol.* 2000;95:726-731.
6. Greendale GA, Reboussin BA, Hogan P, et al. Symptom relief and side effects of postmenopausal hormones: results from the Postmen-

- opausal Estrogen/Progestin Interventions Trial. *Obstet Gynecol.* 1998;92:982-988.
7. Wiklund I, Berg G, Hammar M, et al. Long-term effect of transdermal hormonal therapy on aspects of quality of life in postmenopausal women. *Maturitas.* 1992;14:225-236.
8. Elia D, Tamborini A, Leomach Y, et al. Efficacy and tolerability of low dose of Oesclim (25 mcg daily) in the management of symptomatic menopausal women: a French open-label study. *Curr Med Res Opin.* 2000;16:94-106.
9. Utian WH, Shoupe D, Bachmann G, et al. Relief of vasomotor symptoms and vaginal atrophy with lower doses of conjugated equine estrogens and medroxyprogesterone acetate. *Fertil Steril.* 2001;75:1065-1079.
10. MacLaren A, Woods NF. Midlife women making hormone therapy decisions. *Womens Health Issues.* 2001;11:216-230.
11. Wilhite LA, O'Connell MB. Urogenital atrophy: prevention and treatment. *Pharmacotherapy.* 2001;21:464-480.
12. Stadberg E, Mattsson LA, Milsom I. The prevalence and severity of climacteric symptoms and the use of different treatment regimens in a Swedish population. *Acta Obstet Gynecol Scand.* 1997;76:442-448.
13. Bachmann GA, Leiblum SR, Kemmann E, et al. Sexual expression and its determinants in the post-menopausal woman. *Maturitas.* 1984;8:19-29.
14. Semmens JP, Tsai CC, Semmens EC, et al. Effects of estrogen therapy on vaginal physiology during menopause. *Obstet Gynecol.* 1985;66:15-18.
15. Laumann EO, Paik A, Rosen RC. Sexual dysfunction in the United States: prevalence and predictors. *JAMA.* 1999;281:537-544.
16. Sarrel PM. Effects of hormone replacement therapy on sexual psychophysiology and behavior in postmenopause. *J Womens Health Gend Based Med.* 2000;9:S25-S32.
17. Sarrel PM. Sexuality and menopause. *Obstet Gynecol.* 1990;75:26S-30S.
18. Nathorst-Boos J, Wiklund I, Mattsson LA, et al. Is sexual life influenced by transdermal estrogen therapy? A double blind placebo controlled study in postmenopausal women. *Acta Obstet Gynecol Scand.* 1993;72:656-660.
19. Raz R, Stamm WE. A controlled trial of intravaginal estriol in postmenopausal women with recurrent urinary tract infections. *N Engl J Med.* 1993;329(11):753-756.
20. Eriksen B. A randomized, open, parallel-group study on the preventive effect of an

- estradiol-releasing vaginal ring (Estring) on recurrent urinary tract infections in postmenopausal women. *Am J Obstet Gynecol.* 1999;180:1072-1079.
21. Urinary incontinence in adults. NIH Consensus Statement Online. October 3-5, 1988; 7(5):1-32. Available at: http://consensus.nih.gov/cons/071/071_statement.htm#1.What_Is. Accessed March 10, 2003.
22. Fantl JA, Cardozo L, McClish DK. Estrogen therapy in the management of urinary incontinence in postmenopausal women: a meta-analysis. First report of the Hormones and Urogenital Therapy Committee. *Obstet Gynecol.* 1994;83:12-18.
23. Domm JA, Parker EE, Reed GW, et al. Factors affecting access to menopause information. *Menopause.* 2000;7:62-67.
24. Oldenhav A, Jaszmann LJ, Haspels AA, Everaerd WT. Impact of climacteric on well-being. A survey based on 5213 women 39 to 60 years old. *Am J Obstet Gynecol.* 1993;168:772-780.
25. Derman RJ, Dawood MY, Stone S. Quality of life during sequential hormone replacement therapy—a placebo-controlled study. *Int J Fertil Menopausal Stud.* 1995;40:73-78.
26. Wiklund I, Karlberg J, Mattsson LA. Quality of life of postmenopausal women on a regimen of transdermal estradiol therapy: a double-blind placebo-controlled study. *Am J Obstet Gynecol.* 1993;168:824-830.
27. Tosteson AN, Gabriel SE, Kneeland TS, et al. Has the impact of hormone replacement therapy on health-related quality of life been undervalued? *J Womens Health Gend Based Med.* 2000;9:119-130.
28. Hlatky MA, Boothroyd D, Vittinghoff E, et al. Quality-of-life and depressive symptoms in postmenopausal women after receiving hormone therapy. Results from the Heart and Estrogen/Progestin Replacement Study (HERS) trial. *JAMA.* 2002;287:591-597.
29. Hays J, Ockene JK, Brunner RL, et al. Effects of estrogen plus progestin on health-related quality of life. *N Engl J Med.* 2003;348. (Early release article. Available at: <http://content.nejm.org/>. Accessed March 18, 2002.
30. The North American Menopause Society. Amended report from the NAMS Advisory Panel on Postmenopausal Hormone Therapy. *Menopause.* 2003;10:6-12.
31. Bech P, Munk-Jensen N, Obel EB, et al. Combined versus sequential hormonal replacement therapy: a double-blind, placebo-controlled study on quality of life-related outcome measures. *Psychother Psychosom.* 1998;67:259-265.