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FOR CLINICIANS WHO PROVIDE CARE FOR WOMEN

Hormones & Female Sexual Dysfunction in Postmenopausal Women



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SEXUAL FUNCTION & DYSFUNCTION

Sexual dysfunction is a common problem for women of all ages, but following menopause its evaluation and management differ from that of younger women, since the etiology is often linked to the diminished levels of sex hormones. Sexual functioning remains an important aspect of women's health in the postmenopausal years, and sexual dysfunction can greatly reduce quality of life.¹ In recent years, this field has received more attention, and several studies have advanced our understanding of the factors and elements that may be involved. Nevertheless, knowledge of the complex mechanisms driving the female sexual response remains extremely limited. The traditional well-established model of the human sexual response, proposed by Masters and Johnson,² describes a linear progression from excitement to orgasm and resolution. However, more recently, investigators have suggested that the female response may be different and consists of a number of components connected in a cyclic fashion.³ Decline in any of the components may disrupt the cycle and cause sexual dysfunction. Thus, disruption of emotional intimacy with a partner may

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result in loss of desire. Similarly, dyspareunia may lead to loss of desire and difficulty in achieving sexual arousal.

Evaluation and diagnosis of female sexual dysfunction (FSD) continues to be a challenging task for the practicing physician. The process is compromised by the absence of validated physiologic tests. However, recently revised guidelines for the classification of FSD are now available to help establish an appropriate diagnosis.⁴ This classification separates the disorder into four major categories: sexual desire disorder, sexual arousal disorder, orgasmic disorder, and sexual pain disorders.

Postmenopausal women may present with any of the above types of FSD. However, the most common complaints are dyspareunia, diminished sexual desire, and difficulty becoming aroused.

Although age is an independent predictor for FSD, it appears that the menopausal transition is a more important risk factor.⁵ In a cohort of Australian women followed prospectively, menopause resulted in a significant decline in multiple aspects of sexual functioning. Increases in vaginal dyspareunia and decreases in libido were most prominent in this population.⁵ Although the mechanism for this deterioration in sexual function associated with menopause remains uncertain, the decreases in estrogen and androgens have both been implicated. Thus, both estrogen and androgen

FROM THE EDITOR

David F. Archer, M.D.

Please accept our apologies for the delay in getting this issue of *Menopausal Medicine* to you. We hope that it has been worth the wait.

Dr. George Kovalevsky provides an interesting view of Female Sexual Dysfunction and Hormones in postmenopausal women. Sexual dysfunction is a common problem in postmenopausal women and one that is often challenging for the clinician to manage. Dr. Kovalevsky reviews the current understanding of the role that sex hormones play in sexual function in this population. He also discusses how various hormonal therapies impact sexual function and makes recommendations regarding possible treatments.

Dr. James H. Liu discusses the Women's Health Initiative hormone trial results regarding the effects of estrogen plus progestin on bone density and fracture outcomes. The WHI trial provided us with positive findings regarding bone loss and prevention of fracture, most importantly that the use of hormone therapy in women not at risk for osteoporosis results in a significant reduction of fractures. It is important to note that the WHI trial found there was improvement in bone density with lower doses of estrogen and progestin. Dr. Liu takes the original approach of a Question and Answer forum, with questions that the physician might ask or that the physician might hear from patients.

Also included in this issue is a new ASRM Practice Committee report titled "Estrogen and Progestogen Therapy in Postmenopausal Women."

Menopausal Medicine

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replacement, as well as other hormonal therapies, have been studied as potential treatments for FSD in postmenopausal women.

ESTROGEN

The importance of estrogens in sexual function remains controversial. However, some studies have shown that the decline in sexual function at menopause correlates with estradiol levels and not with androgen levels.⁶ Since it is well established that menopause leads to vaginal atrophy, it is not surprising that vaginal dyspareunia is a common problem. It would also follow that sexual arousal, which includes vaginal engorgement and lubrication, would be impaired. Indeed, using vaginal photoplethysmography, it has been demonstrated that postmenopausal women exhibit diminished vaginal engorgement.⁷ However, these findings have not been consistently reproduced. The relationship between estrogen levels and sexual desire appears most tenuous. While it is possible that desire is directly related to estrogen levels, it is also possible that the significant decrease in desire at menopause is secondary to vaginal dyspareunia and impaired arousal, which are the direct consequences of diminished estrogen.

Several clinical trials have been carried out to evaluate the effect of estrogen replacement on FSD. Most of these have demonstrated a significant improvement in sexual function.⁸ Sherwin et al conducted a controlled randomized trial comparing use of conjugated equine estrogen alone with its use in combination with medroxyprogesterone acetate. They found that during the two weeks of estrogen administration alone, sexual desire and arousal were significantly improved.⁹ On the other hand, in their earlier work the authors concluded that estrogens were not related to sexual motivation.¹⁰ Using a randomized crossover trial design, Dennerstein et al also demonstrated that ethinyl estradiol had beneficial effects on sexual desire, enjoyment, vaginal lubrication, and orgasmic frequency in women who had undergone hysterectomy and bilateral oophorectomy.¹¹ However, the authors noted that they observed large interpatient variability. Thus, it appears that only a subset of women will experience a beneficial effect on sexual function with use of estrogen replacement.

If vaginal dyspareunia caused by atrophy is a major cause of sexual dysfunction,

it would follow that vaginal administration of estrogen would be a successful treatment strategy. In women with vaginal atrophy, it has been shown that use of vaginally administered estrogen can improve sexual function. In one clinical trial of the 17-estradiol vaginal ring, significant improvement was observed in dyspareunia, sexual enjoyment and satisfaction.¹² However, no evaluation of the effects of vaginally administered estrogen in women with sexual dysfunction other than dyspareunia has been performed.

ESTROGEN PLUS PROGESTIN

Since it has been observed that unopposed estrogen increases the risk for endometrial hyperplasia and endometrial cancer, progestins have been a necessary adjunct to estrogen replacement in women with a uterus. However, it has been suggested that progestins may have an adverse effect on sexual functioning. The proposed mechanisms for this effect involve inhibition of androgenic activity. These include inhibition of androgen binding to its receptor and inhibition of 5 α -reduction of testosterone to dihydrotestosterone. This effect may be especially pronounced in women receiving estrogen because the estrogen causes an increase in the levels of sex hormone binding globulin, thereby decreasing the levels of bioavailable testosterone. Alternatively, the adverse effect on sexual function may be secondary to the mood dampening effect of progestins. The adverse effect of progestins on mood has been shown in clinical trials.^{9,13}

Trials comparing the use of estrogen replacement alone with use of combined estrogen and progestin therapy have suggested that the addition of progestin may have an inhibitory effect.¹¹ The Women's Health Initiative attempted to evaluate the effect of combination estrogen and progestin therapy on sexual function in postmenopausal women not selected on the basis of any symptoms of sexual dysfunction. Unfortunately, investigation of this variable was limited to a single question with a four-point response scale: very unsatisfied, a little unsatisfied, somewhat satisfied, and very satisfied. No difference in sexual satisfaction was found between treatment and placebo; however, this approach is clearly inadequate as a method for assessing change in such a complex aspect of human function.¹⁴ Based on the available evidence, it remains unclear whether estrogen replacement offers bene-

fit to sexual function beyond improvement in vaginal vascularity and lubrication. Furthermore, it is even less clear whether the addition of progestin has a negative effect.

ANDROGENS

Although understanding of the role played by androgens in female sexual function remains incomplete, it is widely accepted that androgens exert an important influence on sexual function. In particular, androgen levels have been linked with sexual desire¹⁰. Recently, Lobo et al demonstrated a significant association between female sexual desire and concentrations of bioavailable testosterone in postmenopausal women.¹⁵ After menopause, a progressive decline in both ovarian and adrenal androgen production occurs. This effect is most dramatic in women undergoing bilateral oophorectomy. Furthermore, use of estrogen replacement further decreases the amount of bioavailable androgens by increasing the levels of sex hormone binding globulin, thereby further lowering the amount of bioavailable testosterone. Thus, postmenopausal women are at risk for androgen deficiency.

A number of clinical trials have investigated the effect of various preparations and routes of administration of androgen replacement on female sexual function. Sherwin et al conducted the first controlled trial of androgen administration. Their population consisted of 53 women undergoing hysterectomy and bilateral oophorectomy. Preoperatively, subjects received an intramuscular injection and were randomly assigned to either estrogen plus androgen, estrogen alone, androgen alone (200mg testosterone enanthate), or placebo. After three months, subjects received one month of placebo and then were crossed over to another treatment. The study demonstrated that androgen administration enhanced sexual desire but did not have any effect on physiologic responses or orgasm.¹⁰

Other investigations have also produced evidence indicating an important role for androgens in female sexual functioning. Sarrel et al recruited 20 postmenopausal women using estrogen replacement, with or without a progestin, who were dissatisfied with the results. They were randomized to either 1.25mg of esterified estrogens daily alone or in combination with 2.5mg of methyltestosterone. The study found that after four and eight weeks of product use, women receiving the combi-

nation therapy reported significantly improved sexual sensation and desire in comparison with women receiving estrogen alone.¹⁶

Shifren et al recruited 75 women who had undergone hysterectomy and bilateral oophorectomy, were using conjugated equine estrogens at a dose of 0.625mg per day or higher, and reported having impaired sexual function. Each subject received three treatments administered in random order: placebo, 150mg, and 300mg of testosterone per day transdermally for 12 weeks each. The authors found that despite a strong placebo response, treatment with the higher dose of transdermal testosterone resulted in a significant improvement in sexual function. A statistically significant difference from placebo was present only in the domains of frequency of sexual activity and sexual pleasure-*orgasm*.¹⁷

Most recently, Lobo et al conducted a multicenter randomized trial using postmenopausal women on estrogen replacement who reported hypoactive sexual desire with the onset of menopause. Two hundred twenty-one subjects were randomized to receive daily either 0.625mg of esterified estrogens and 1.25mg of methyltestosterone or 0.625mg of esterified estrogens alone for 16 weeks. The authors reported that addition of methyltestosterone resulted in significant increases in level of sexual desire, frequency of desire, and responsiveness. The study also showed that the androgen treatment was well tolerated with no significant changes in acne or hirsutism, but a 17.5% decrease in HDL cholesterol was observed. This well-designed trial was also the largest and had the longest follow-up period of any such effort.¹⁵

Dehydroepiandrosterone (DHEA) is a weak androgen that has received much publicity and is available in the United States without a prescription. DHEA production by both the adrenal gland and the ovary decreases with age. In postmenopausal women, peripheral conversion of DHEA and DHEAS, the sulfated form, produced by the adrenals is the major source of serum testosterone.¹⁸

Although controlled trials in postmenopausal women are lacking, preliminary evidence suggests that DHEA therapy may be beneficial in treatment of FSD. Arlt et al performed a randomized, placebo-controlled, crossover study of 50mg daily administration of DHEA for four

months in 24 women with adrenal insufficiency. They found that treatment resulted in a significant improvement in sexual interest, frequency of sexual thoughts, and sexual satisfaction.¹⁹ Conversely, Barnhart et al conducted a randomized, placebo-controlled trial of 60 perimenopausal women with complaints of diminished well-being, mood, or libido. Subjects received 50mg of DHEA daily or placebo for three months. The authors reported a significant increase in serum DHEA, DHEAS, and testosterone, but a significant change in libido or well-being was not seen.²⁰ However, these were perimenopausal women without evidence of androgen deficiency.

In summary, clinical trials in postmenopausal women with FSD have consistently demonstrated that addition of androgens to estrogen replacement results in a significant improvement of sexual function, particularly sexual desire. Since sexual function is complex and influenced by multiple variables, not all women will benefit from androgen supplementation. Those with clear androgen deficiency are most likely to experience an improvement. The incidence of adverse side effects appears acceptable, but larger studies with long-term follow up are necessary to fully assess the risks of such therapy.

SELECTIVE ESTROGEN RECEPTOR MODULATORS

Tamoxifen and raloxifene are the two selective estrogen receptor modulators (SERM) commonly used by menopausal women. Use of tamoxifen has been linked to female sexual dysfunction. Most studies of the effects of tamoxifen on sexual function have been performed in breast cancer survivors. These studies are difficult to interpret because of the confounding influence of the disease itself as well as other treatments such as chemotherapy, which often results in ovarian failure. Although limited, most studies have shown that tamoxifen appears to impair sexual function in breast cancer survivors.

Only two studies have addressed the effect of tamoxifen on sexual function in women without breast cancer. The health-related quality of life (HRQL) component of the NSABP P-1 trial found that tamoxifen caused sexual dysfunction in some women.²¹ Specifically, the authors reported significant increase of problems in sexual interest, arousal, and orgasm. In this analysis, they did not control for menopausal

status. They did find that pain with intercourse was significantly increased among tamoxifen users 35 to 49 years of age only.²¹ The second study addressing this issue found no adverse effect.²² However, this study was highly vulnerable to confounding by two major factors. First, the investigators did not control for menopausal status, and more than two-fifths of the women who were premenopausal at baseline became perimenopausal during the study. Second, the analysis did not control for other hormone use, and two-fifths of women used hormone replacement therapy during the trial²².

In evaluating the effects of tamoxifen on sexual function, most of the investigations have focused on its effects on the vagina. From the available data, it appears that estrogen levels exert an important control over the type of effect that tamoxifen has on female genital tissues. Tamoxifen is a SERM and as such exhibits estrogenic or anti-estrogenic action depending on the tissue. In the vagina, tamoxifen appears to act as a weak agonist. In an estrogen-poor environment, i.e., menopausal women, it appears to have a positive effect on vaginal tissue. On the other hand, in an estrogen-rich environment, i.e., reproductive-age women and women taking hormone replacement therapy, it appears to cause vaginal dryness and a decrease in the maturation index.²³ Several studies have confirmed that tamoxifen has an estrogenic effect on the vaginal epithelium and induces its maturation in postmenopausal women.²³ Thus, while tamoxifen may have an adverse effect on sexual function in premenopausal women, the opposite may be true for postmenopausal women.

The best available data regarding the effect of raloxifene on sexual function comes from the Multiple Outcomes of Raloxifene Evaluation (MORE) trial. This study enrolled postmenopausal women with osteoporosis and randomized them to either raloxifene at 60mg per day, 120mg per day, or placebo. Nine hundred forty-three women, a subset of the larger population, were asked to complete a sexual function questionnaire at baseline and again after 36 months of treatment. This study found no difference between the treatment and placebo groups in any of the aspects of sexual function.²⁴ Two other clinical trials have addressed the effect of raloxifene on quality of life in postmenopausal women. These trials evaluated sexual function only superficially as one of many components

of a broad survey and found that raloxifene had no significant effect.^{25, 26}

TIBOLONE

Tibolone is a synthetic steroid with tissue-specific estrogenic, progestagenic, and androgenic properties and is not available in the United States. Because of tibolone's unique and complicated mechanism of action, it is difficult to theorize about its potential effect on sexual function; however, it would seem plausible that a combined estrogenic and androgenic effect would be beneficial. Indeed, several clinical trials that addressed sexual functions all found that tibolone improved sexual function. Recently, Laan et al conducted a randomized, placebo-controlled, crossover study in 38 postmenopausal women. They reported that treatment resulted in significantly improved vaginal blood flow, sexual desire, and arousability.²⁷

In another trial of 120 surgically menopausal women, Castelo-Branco et al randomized subjects to four groups: 1) 4mg estradiol valerate plus 200mg enanthate of dihydroandrosterone IM monthly, 2) 50mg/day of transdermal 17 β -estradiol continuously, 3) 2.5mg tibolone daily, or 4) no treatment. All treatment groups were found to have improvement in several aspects of sexual function, but the tibolone and estradiol + dihydroandrosterone groups displayed a significantly greater improvement than estradiol alone.²⁸

CONCLUSIONS

The female sexual response is a complicated mechanism that may be adversely affected by the onset of menopause. The two most common sexual function problems reported by postmenopausal women are vaginal dryness and diminished sexual desire. Our understanding of female sexual function and dysfunction remains limited, but existing data allow for some preliminary conclusions. It appears that lack of estrogen may lead to sexual dysfunction primarily by causing vaginal atrophy and dyspareunia. These symptoms may be treated by systemic or local estrogen therapy. On the other hand, androgen deficiency appears to be most strongly linked to diminished sexual desire. Growing evidence indicates that administration of androgens may be beneficial in such situations. Tamoxifen has been associated with FSD, although this relationship remains unclear, and it may actually be beneficial in postmenopausal women. Raloxifene does not seem to have a major influence on

sexual function. Finally, tibolone appears to exert a beneficial effect; however, the mechanisms of this action are not certain.

Having learned the lessons of the pitfalls of estrogen replacement therapy, caution is advised in prescribing any of the above therapies since long term, large-scale clinical trials have not yet been undertaken. Therapy should be considered on an individual basis, and the benefits and risks should be weighed in view of the available scientific evidence.

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The author has revealed the following potential conflict of interest: Wyeth Speakers' Bureau.

Estrogen Therapy and Fractures: Lessons After the WHI



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The Women's Health Initiative (WHI) hormone trial is the first large, prospective randomized trial to study the effect of estrogen and progestin (E+P) on bone density and fracture outcomes.¹ When this study was stopped early after a mean of 5.2 years of treatment, the E+P group had a 34% overall reduction in hip fractures; a 34% reduction in clinical vertebral fractures; and a relative risk reduction of 24% for other fractures. Because the WHI E+P trial had over 16,600 subjects, bone density was performed at only five of the 40 study sites. The bone density results will be analyzed and reviewed in a latter publication.

In contrast to other clinical trials that focus on fracture reduction, these impressive reductions in fracture risk associated with E+P use in the WHI trial were achieved in a low-risk menopausal population. The WHI population was composed of younger women (mean age of 63.2

years) who were less likely to have low bone mass. Thus, after five years of E+P therapy, the reduction in fracture risks at the hip and spine sites are quite similar to the 30% to 48% that is reported in randomized trials for alendronate,² risedronate,³ and raloxifene.⁴

Despite the benefits of E+P on bone conservation and reduction in colon cancer risks, the overall risks of E+P therapy on cardiovascular disease endpoints and breast cancer outweighed its benefits. Thus, the Food and Drug Administration has recommended the E+P therapy be used primarily for reduction of menopausal symptoms. In patients with both menopausal symptoms and osteoporosis, the American College of Obstetricians and Gynecologists has recommended that E+P therapy would be appropriate. E+P therapy should be used at the lowest possible dose for a short period of time. These recommendations have led to a significant shift in menopausal hormone therapy use by physicians and patients. As a result, the WHI findings raise additional new challenges in our treatment approach(es) for postmenopausal women.

What happens to bone density and fracture risk if hormone therapy is discontinued after years of hormone therapy?

With institution of estrogen therapy, bone mineral density (BMD) is stabilized or slightly increased. Lindsay et al⁵ was the first to demonstrate in a longitudinal study that discontinuation of estrogen leads to a rapid and progressive loss in bone density at a rate that is similar to the early menopausal period. Current evidence suggests a decline in spine BMD of $-1.6 \pm$

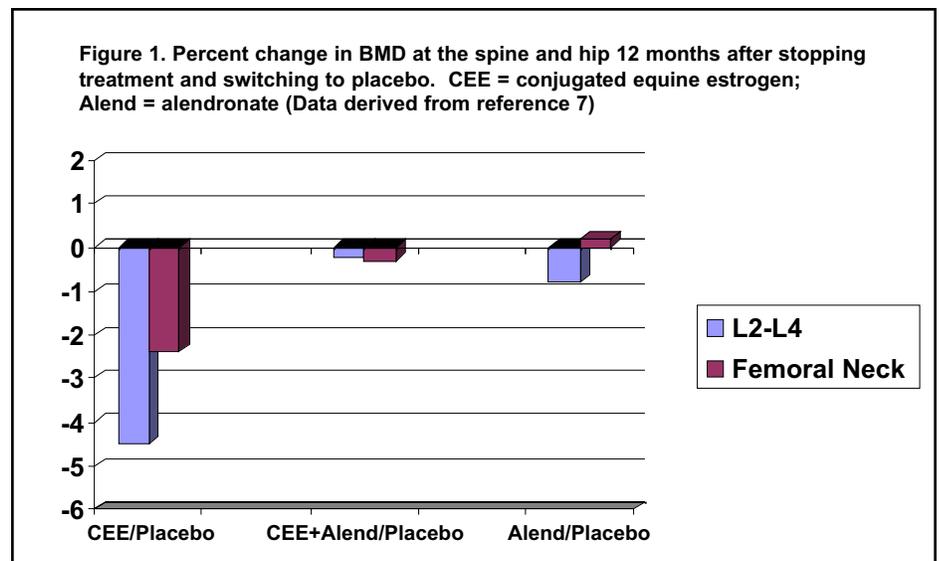


Table 1: Minimal estrogen dose required for prevention of osteoporosis.

Compound	Minimal Established Dose
Conjugated estrone ⁹	0.3 mg/day
Conjugated equine estrogen ¹⁰ (CEE)	0.3 mg/day
Oral micronized estradiol	0.5 mg/day
Trandermal estradiol ¹¹	0.025 mg/day
Ethinyl estradiol ¹²	5 µ/day

How should I monitor patients on low-dose hormone therapy?

Bone biomarkers can be used to follow acute responses to therapy. Bone markers are not useful for establishing the diagnosis of osteoporosis and should not be used in isolation to make therapeutic decisions. After low-dose hormone therapy has been initiated or the estrogen dose is lowered, the goal would be for the bone resorption marker urinary N-telopeptide (NTx) to be in the lower half of the premenopausal range within three to six months. It is not necessary to do serial measurements. If the NTx remains elevated, one should check for treatment compliance and should consider an additional evaluation for secondary causes for bone loss.

Will bone mineral density increase on low-dose hormone therapy?

Changes in bone mineral density are not seen acutely but should become evident by 12 to 24 months of treatment. In randomized clinical trials, increases in lumbar BMD of approximately 3% were observed at the end of 3.5 years with 0.3 mg/day oral CEE;¹⁰ 2% increases were noted over two years in the HOPE trial;¹³ while with 0.025 mg/day of trandermal estradiol, spine BMD increased approximately 1% over the two-year study interval.

What about combination therapy with low-dose estrogen and a bisphosphonate?

Combination therapy with estrogen (0.625 mg/day of CEE) and alendronate (10 mg/day) have been studied in small clinical

1.3% during the first two years after stopping estrogen with a slower rate of loss of $-0.83 \pm 1.35\%$ in subsequent years.⁶ A second similar study by Greenspan et al suggests an even greater loss in BMD of -4.5% at the lumbar spine during the first year after stopping estrogen.⁷ Figure 1 shows the effects of acute estrogen withdrawal from data derived from the Greenspan study.

In summary, it appears that women who choose to discontinue hormone therapy are at increased risk for rapid loss in BMD and subsequent development of low bone mass and osteoporosis. These and other risk factors for development of osteoporosis such as smoking, thin body habitus, and white or Asian ethnicity should be considered in counseling women who plan to discontinue hormone therapy.

How should bone status be monitored in patients discontinuing hormone therapy?

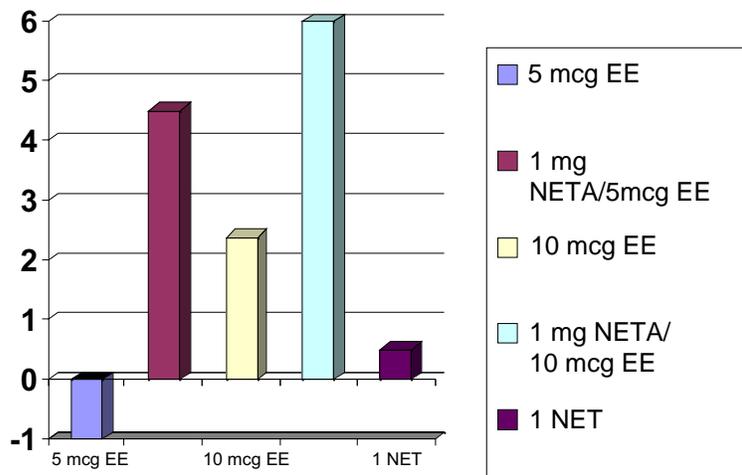
The “gold standard” for assessment of fracture risk is a dual energy x-ray absorptiometry (DEXA) scan to determine BMD of the hip and spine. Normative BMD databases for young adult women based on race have been developed by the DEXA manufacturers and also by the NHANES III study. The T-score is used to compare the patient’s BMD measurement to a young adult mean control group and represents the standard deviation score from the young normal mean value. AT-score of greater than -1 indicates that the patient’s BMD is more than 1 standard deviation below the young adult value and is used to define osteopenia or low bone mass. AT-score of greater than or equal to -2.5 is used to define osteoporosis. For each stan-

dard deviation below the young adult value, there is a 2.3- 2.6-fold increase in fracture risk.⁸ It is important to remember that the majority of fractures occur in patients between T-scores of -1 to -2.5 .

If patients choose to start or switch to low-dose hormone therapy, what are the minimal estrogen doses that are clinically effective?

A number of studies have focused on reducing the doses of estrogen required for bone-conserving activity. These dosages are provided in Table 1. In most of these clinical trials, subjects received supplemental calcium at a daily dose of approximately 500mg/day to 1000 mg/day with adequate vitamin D intake. In addition, in several of the trials, up to 20% of subjects were found to have decreased BMD or failed to respond to the minimal estrogen dose utilized.

Figure 2. Percent change in BMD at L2-L4 after two years of treatment with ethinyl estradiol (EE) alone; in combination with norethindrone acetate (NETA) or with norethindrone alone (NET). Data do not constitute a head to head comparison and are derived from references 12 and 14.



trials.¹³ These studies indicate that BMD increases are greater than with either estrogen or alendronate alone. However, the combination of a low-dose estrogen therapy with a bisphosphonate has not been evaluated. Moreover, reliable fracture endpoint data are not available. Because of these issues, this approach should be carefully considered by physicians with extensive experience in this area.

Does the type of progestin used with estrogen impact on bone density?

In most clinical trials, progestins have been used in combination with a variety of estrogens to prevent endometrial hyperplasia and to induce endometrial thinning and amenorrhea. The two most commonly utilized progestins in the United States are medroxyprogesterone acetate (MPA) and norethindrone acetate (NETA). Current evidence suggests that NETA can reduce bone loss independent of estrogen^{12,14} and may have additive effects on BMD when combined with estrogen. Figure 2 shows the effects of NETA on bone density from these two such studies.

SUMMARY

The WHI results have made a significant impact in our management of the menopause patient. For those patients who choose to stop estrogen, the long-term impact on bone health must be monitored and alternative therapies considered. In selected patients who continue on low dose estrogen therapy for vasomotor symptoms or other reasons, it is important to consider the minimal dose required for bone protection as well as the proper selection of the type of progestin.

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ESTROGEN AND PROGESTOGEN THERAPY IN POSTMENOPAUSAL WOMEN

The Practice Committee of the American Society for Reproductive Medicine

(Editor's Note: Prepared prior to the stopping of the estrogen-only arm of the Women's Health Initiative)

Hormone therapy (HT) can be used to treat or prevent problems associated with the decline in estrogen production by the ovaries after menopause. Menopause occurs naturally when the ovarian follicles are depleted or following surgical removal of both ovaries. The resulting hypoestrogenic state may adversely affect estrogen target tissues, which include the brain, skeleton and skin, as well as the cardiovascular and genitourinary systems. The concentration and function of hormone receptors varies in these organs and systems; differences in genetics, body mass index, and body habitus also may influence the levels of endogenous estrogen and androgen in postmenopausal women. Significant variability among women exists with regard to their development of menopausal symptoms, the reaction of their target tissues to estrogen deficiency, and in their response to HT.

GOALS OF THERAPY

There are two broad categories of menopausal hormone therapy: estrogen alone therapy (ET) and estrogen combined with progestogen therapy (E/PT). For the purposes of this document, progestogen refers to natural progesterone as well as synthetic congeners of progesterone (progestins).

The goals of menopausal hormone therapies are to:

- a. reduce symptoms resulting from estrogen depletion, including hot flashes, sleeplessness, lethargy, depressed mood, and vaginal dryness;
- b. treat urogenital atrophy; and
- c. prevent osteoporosis.

Although ET and E/PT may improve a woman's quality of life, each woman has a unique risk profile which might lead to more, or less, benefit from HT. Patient preferences as well as evidence from medical research influence management decisions. As a result, an unwavering policy applied to all menopausal women will not meet the individual needs of many women. Health care providers should therefore consider how the benefits and risks may affect each patient before drawing conclusions or recommending HT. In addition, the balance between risks and benefits, compliance with therapy, and side effects needs to be periodically reassessed, and newly published research findings must be incorporated into patient care decisions.

ESTROGEN DEFICIENCY SYMPTOMS

The principal symptom of the early menopausal years is the vasomotor (hot) flush. Hot flushes and night sweats are experienced by 50% to 85% of postmenopausal women and cause significant distress to approximately 25%. Sleep disturbances caused by nocturnal hot flushes and sweating can lead to lethargy and depressed mood, although depression is equally common in premenopausal and postmenopausal women. Vasomotor symptoms are more common and more severe after a surgical menopause. The frequency of hot flushes decreases with time: in the Postmenopausal Estrogen/Progestin Interventions (PEPI) trial, the percentage of women taking placebo who experienced vasomotor symptoms declined from 56% at baseline to 30% in year three.¹ Only a small percentage of women continue to suffer from vasomotor flushes 10 years after their menopause. Fifteen years after menopause approximately 3% of women report very frequent hot flushes and 12% report moderate to severe hot flushes.^{2,3}

HT is the most effective treatment for hot flushes and also decreases sleep disturbances, thereby improving quality of life. The value of such treatment has been demonstrated in numerous randomized controlled trials (RCTs). One of these, the three-year PEPI trial, involved 875 menopausal women who were randomly allocated to one of five treatments. The treatments were placebo, estrogen alone (conjugated equine estrogens [CEE]), estrogen plus cyclic progestogen (either medroxyprogesterone acetate [MPA] or micronized progesterone) or estrogen plus continuous progestin (medroxyprogesterone acetate). All hormone treatments were more effective than placebo in reducing hot flushes. There were no significant differences between the treatments, and the

size of the treatment effect became smaller after the first year. For instance, the likelihood of having severe vasomotor symptoms was approximately 78% lower in the four active treatment groups compared with the placebo group during the first year of treatment (summary RR 0.22, 95% CI, 0.17-0.30), and approximately 60% lower during the third year of treatment (summary RR 0.40, 95% CI, 0.30-0.53). For every two patients treated during the first year,

“The principal symptom of the early menopausal years is the vasomotor (hot) flush.”

one reported fewer severe vasomotor symptoms, but during the third year when the placebo group was experiencing fewer symptoms, the number needed to treat (NNT) rose to six patients. In summary, HT reduces vasomotor symptoms, the benefit compared to placebo is more dramatic during the first year of treatment, and cyclic or continuous progestogen does not add to or subtract from the estrogen effect to an extent that can be measured. RCTs in younger postmenopausal women have demonstrated similar improvement in the severity and frequency of hot flushes and an improvement in the quality of life.^{4,5}

In earlier trials, estrogen increased feelings of well-being, while combinations with progestin attenuated the impact of estrogen on behavioral effects.^{6,7} In the PEPI trial, however, cognitive-affective symptoms such as forgetfulness (present in 34% of subjects at baseline), feeling easily distracted (25%), and difficulty concentrating (24%) were not changed with ET or E/PT after one year or three years of treat-

ment. Symptoms of anxiety were present in only 5% at baseline and were unchanged over three years in each arm of the PEPI trial.

The Women's Health Initiative (WHI) primary prevention trial of continuous combined E/PT was not designed to evaluate management of menopausal symptoms. Nevertheless, quality-of-life measures were collected at baseline and at one year in all women and at three years in a subgroup of 1,511 of the 16,608 women randomized to receive placebo or E/PT. In a post-hoc subgroup analysis, randomization to E/PT resulted in no significant effects on general health, vitality, mental health, depressive symptoms, or sexual satisfaction, and a small but significant benefit for sleep disturbance, physical functioning, and bodily pain after one year. At three years, there were no significant benefits in any quality-of-life outcomes. Among women 50 to 54 years of age with moderate-to-severe vasomotor symptoms at baseline, E/PT improved vasomotor symptoms and resulted in a small benefit in terms of sleep disturbance but no benefit in terms of the other quality-of-life outcomes.³

Results observed in the Heart and Estrogen/progestin Replacement Study (HERS), a secondary prevention trial comparing E/PT with placebo, contrast with those from the WHI. HERS demonstrated that the effect of HT on health-related quality of life measures depended upon the presence or absence of menopausal symptoms at baseline. Study participants were on average 18 years postmenopausal, with a mean age of 67 years. HT reduced hot flashes, trouble sleeping, and vaginal dryness more than placebo, and the benefit was more marked in younger women who were symptomatic at study entry.²

An important knowledge gap in this area concerns the differential risk of cardiovascular disease, osteoporosis, and cancer for women who have estrogen deficiency symptoms compared with those who do not experience such symptoms, because women with severe hot flushes were largely excluded from participation in the WHI. Women who experience significant vasomotor symptoms tend to be thinner and have lower endogenous estrogen levels. In a single large cohort study of elderly postmenopausal women, cardioprotective effects were limited to women who had a lower body mass index.⁸ Most studies, however, have insufficient power to perform comprehensive subgroup analyses.

UROGENITAL SYMPTOMS

Estrogen is an effective treatment for symptoms of urogenital atrophy, such as vaginal dryness and sexual discomfort. A

meta-analysis of 10 randomized placebo-controlled trials found significant improvement in all outcomes evaluated: dyspareunia, related symptoms, and the physician's assessment.⁹ The vaginal route of administration achieved better symptomatic relief than oral, transdermal, or parenteral routes of administration. Few of the studies included in the analysis evaluated whether treatment benefits continued after six months.

Estrogen also has been recommended for the treatment of urinary incontinence, a problem that affects 5% to 14% of women age 60 years or older. The presence of estrogen receptors in urethral mucosa and smooth muscle suggests that estrogen alone might improve symptoms of urinary incontinence. In a meta-analysis including five RCTs involving a total of 117 subjects, subjective improvement in symptoms of urinary incontinence was significantly greater with ET compared to placebo treatment.¹⁰ However, HERS reported contrasting results from a considerably larger trial; among 1,525 participants who reported at least one episode of urinary incontinence per week, E/PT was associated with a worsening of incontinence symptoms compared to the placebo group.¹¹ After an average follow-up of 4.1 years, incontinence had worsened in 38.4% of the hormone-treated group and 28.4% of the placebo group. The WHI trial involving E/PT did not report on an evaluation of urogenital symptoms. There is a need for studies of the possible mechanisms by which HT might affect stress and/or urgency incontinence and for trials having incontinence as a primary outcome and sufficient power to address effectiveness in clinically important endpoints.

EFFECTS ON BONE

Although RCTs uniformly indicate that HT maintains or improves bone mineral density in the spine, proximal femur and radius,¹² results have not been as consistent with respect to prevention of clinical fractures. The HERS involved 2,763 American women with established heart disease (average age 66.7 years). The interventions were 0.625 mg of conjugated equine estrogens plus 2.5 mg of medroxyprogesterone acetate daily (E/PT) or placebo. After a mean 4.1 years of follow-up, E/PT did not alter significantly the likelihood of hip fracture (RR 1.09, 95% CI, 0.48 - 2.46) or other type of fracture (RR 0.93, 95% CI, 0.73-1.20).¹³ Between 55% and 57% of each group had a body mass index > 27 kg/m². On average, patients enrolled in HERS were 18+8 years postmenopausal and fracture incidence was not a primary outcome measure. In contrast, a Finnish

RCT involving 464 postmenopausal women (average age 52.7 years) with fracture risk as the primary outcome measure yielded different results. Patients were randomly allocated to one of four groups: E/PT alone (estradiol and cyproterone), vitamin D alone, E/PT plus vitamin D, or placebo. After a mean 4.3 years follow-up, and adjusting for baseline bone density and fracture history, the two HT groups had significantly fewer non-vertebral fractures than the two groups not receiving HT (RR 0.43, 95% CI 0.20-0.91).¹⁴ The trial is vulnerable to small sample errors, as there were only three hip fracture events, all in the non-HT groups.

In a Swedish case-control study involving 1,327 women (average age 72.5 years) with hip fractures and 3,262 population controls, the odds ratio for hip fracture among current HT users was 0.35 (95% CI, 0.24, 0.53) and 0.76 (95% CI, 0.57-1.01) for past users. Transdermal formulations of estrogen were as effective as oral estrogens.¹⁵ Since the incidence of hip fracture is less than five per 100,000 women years in women under age 70, studies with a mean age at enrollment below 70 years may have insufficient power to demonstrate a significant benefit. The greater benefit from current use provides a justification for HT use after age 70 when hip fracture incidence is meaningful and if other osteoporosis preventive agents cannot be used or tolerated. Summing up, the bone density outcome trials, the epidemiological data, and the smaller of two fracture outcome trials all suggest that current HT use may prevent clinical fractures.

In the WHI trial there were 10 and 15 hip fractures in the E/PT and placebo groups, respectively, and the relative hazard was 0.66, (adjusted 95% confidence interval 0.33-1.33). Because hip fracture was a secondary outcome, the 95% confidence interval was adjusted for the number of statistical comparisons that were made. The WHI was the first large clinical trial to show a significant overall reduction in osteoporotic fractures (hip, vertebral, and other osteoporotic fractures, including all fractures except those of the ribs, chest/sternum, skull/face, fingers, toes, and cervical vertebrae). Even after adjustment, the hazard ratio for any osteoporotic fracture was significantly reduced in the E/PT group (HR 0.76, 95% CI, 0.63-0.92). The mean age of subjects enrolled in the WHI was 63.3 years. Approximately 85% of osteoporotic fractures observed in the WHI trial were non-vertebral and non-hip fractures.

Because the effect on hip fracture is small, HT treatment is not warranted solely for prevention of hip fractures. Although osteopenia and osteoporosis may be pre-

vented and treated with HT, alternative agents may have a better risk-benefit ratio. Trials are needed to compare other strategies with protocols that include HT treatment.

SENILE DEMENTIA AND COGNITION

More than 33% of women 65 years or older will develop dementia during their lifetime.¹⁶ In a meta-analysis which included two cohort studies and 10 case-control studies, HT was associated with a 34% reduction in the risk of dementia (summary OR 0.66, 95% CI, 0.53-0.82).¹⁷ There was insufficient information in the studies to assess the effect of estrogen or progestogen in formulation, dosage, duration or recency of use. Results of three subsequent epidemiological studies are conflicting but do not change the overall estimate of risk reduction in a meaningful way.^{18,19,20}

Memory loss is the first process to be affected in Alzheimer's disease, but it has been difficult to demonstrate an effect of HT on memory, both in normal women and in women with early dementia. A meta-analysis including nine RCTs and eight cohort studies which employed a variety of cognitive tests in women free of dementia, found that HT was associated with improved verbal memory, vigilance to task, reasoning and motor speed; generally benefits were limited to symptomatic women and were unlikely to be detected in asymptomatic women.¹⁷ Not included in the meta-analysis was a recent report on cognitive function among healthy older women in the Nurses' Health Study cohort;²¹ HT users scored higher in only one of four cognitive tests. The estimated risk of hormone users having a low score on the test of verbal fluency was reduced by 30% (RR = 0.70, 95% CI, 0.45-1.09); results were similar for ET and E/PT. In addition, a three-year prospective study reported that prior HT use and current use of greater than 10 years was associated with a reduced risk of Alzheimer's disease (RR=0.59, 95% CI, 0.36-0.96).²²

In the Women's Health Initiative Memory Study (WHIMS), E/PT increased the risk of dementia among women 65 years and older, and it did not prevent mild cognitive impairment.^{23,24} Compared to placebo, the hazard ratio for probable dementia was 2.05 (95% CI, 1.21-3.48) in women who received E/PT. Approximately 50% of cases were classified as Alzheimer disease in each group. Approximately 12.5% of cases were classified as vascular dementia in the E/PT group compared to 5% in the placebo group. There were 45 and 22 cases of probable dementia observed per 10,000 woman-years in the E/PT and placebo

groups, respectively. Annual assessments of global cognitive function showed no difference between groups. Most women receiving E/PT did not experience clinically relevant declines in cognitive function compared to placebo.

In the WHIMS, cases of probable dementia appeared in the first year of intervention in both the E/PT and placebo groups, suggesting that some subjects had cognitive decline at baseline. E/PT did not improve cognitive function or slow the progression of symptoms and actually appeared to increase progression to probable dementia. The ET arm of the WHIMS continues. Other trials are needed to evaluate effects on memory and cognition among asymptomatic women.

EFFECTS ON CORONARY HEART DISEASE

Cardiovascular disease is the leading cause of death in postmenopausal women. The association between HT and coronary heart disease (CHD) has been evaluated in three types of studies: epidemiological studies (the most common), RCTs evaluating intermediate outcomes, and RCTs evaluating definitive coronary heart disease outcomes, usually nonfatal myocardial infarction (MI) and CHD death.

A summary of epidemiological studies that appeared in a 1996 World Health Organization (WHO) Technical Report published in 1996 suggested that HT use reduced the risk of nonfatal MI or coronary artery disease (CAD) death by 44% (summary RR 0.56, 95% CI, 0.51-0.61) compared to no use.²⁵ In the most recent analysis from the Nurses Health Study, the relative risk of a major coronary event (nonfatal MI or CHD mortality) was lower among current users of HT compared to never-users. After adjustment for cardiovascular risk factors, the relative risk was 0.61 (95% CI, 0.52-0.71).²⁶ Among women taking oral conjugated estrogens, the reduction in risk for 0.3 mg and 0.625 mg daily dosages and for conjugated estrogens plus progesterin was similar.

The results of RCTs that have evaluated intermediate outcomes are less consistent than those observed in epidemiologic studies, but favorable effects of HT on lipid profiles, including lipoprotein (a), have been observed.^{12,27,28,29} HT does not slow the progression of coronary artery atherosclerosis, as estimated by angiographic measurements of coronary artery diameter. In the Estrogen Replacement and Atherosclerosis (ERA) Trial²⁷, angiographic endpoints were used to determine the effect of ET and E/PT on the progression of atherosclerosis in 309 postmenopausal women with documented CAD disease. Neither con-

jugated estrogens alone (0.625 mg per day) nor continuous combined HT (0.625 mg conjugated estrogens plus 2.5 mg medroxyprogesterone acetate per day) affected the progression of coronary atherosclerosis when compared to placebo treatment, even though lipoprotein profiles were improved in both HT groups. The women in the ERA trial were followed for an average of 3.2 years.²⁷ Identical results were found in the Women's Estrogen-progestin Lipid Lowering Hormone Atherosclerosis Regression Trial (WELL-HART) which examined HT regimens utilizing 17 β -estradiol with or without cyclic medroxyprogesterone acetate.⁶⁹

The most valid evidence comes from three large RCTs (HERS, ESPRIT, and WHI) which found no evidence that E/PT (HERS, WHI) or ET (ESPRIT) was effective for primary or secondary prevention of nonfatal MI and CHD deaths.^{13,30,31}

The HERS secondary prevention trial involved 2,763 women with coronary artery disease who were postmenopausal and who had an intact uterus. Women were 55 to 80 years old (mean age 66.7 years).¹³ During an average follow-up of 4.1 years, treatment with oral E/PT (0.625 mg of conjugated equine estrogens plus 2.5 mg of medroxyprogesterone acetate) had no effect on MI or CHD death (relative hazard 0.99; 95% CI, 0.80-1.22). There was a pattern of early increase in CHD events with a time trend towards fewer CHD events in years 4 and 5. HERS II, a follow-up open label observational study of 2.7 years' duration, demonstrated that the lower rates of CHD events among women seen in the final years of HERS did not persist during the additional years of observation. After 6.8 years, E/PT did not reduce the risk of cardiovascular events in women with pre-existing coronary artery disease. The smaller ESPRIT study randomized 1,017 postmenopausal women aged 50 to 69 years of age (mean age 62.6 years) with a recent first MI to placebo or ET (2 mg of estradiol valerate) for two years. The frequency of nonfatal reinfarction or cardiac death did not differ between the two groups (rate ratio 0.99; 95% CI, 0.70-1.41).³¹ The results of HERS and HERS II suggest that E/PT should not be used for secondary prevention of cardiac events in women with CHD. Secondary analysis of HERS identified a substantial underutilization of medications proven effective for secondary prevention by the study participants, such as aspirin, β -blockers, and statins.³² Data from ESPRIT suggests that ET administered soon after recovery from a first MI does not reduce the risk of subsequent cardiac events. A smaller RCT concluded that ET and E/PT do not reduce risk of MI or

CHD death in postmenopausal women hospitalized with unstable angina.³³

In the WHI trial primary prevention trial,³⁰ there were 37 and 30 CHD events per 10,000 woman-years in the E/PT and placebo groups, respectively, yielding a small but significant increase in CHD risk (hazard ratio 1.29, 95% CI, 1.02-1.63). The small increase in CHD occurred despite a significant 12.7% reduction in low-density lipoprotein cholesterol and 7.3% increase in high-density lipoprotein cholesterol with E/PT relative to placebo. Most of the excess CHD risk was nonfatal MI, excluding silent MI (HR 1.30, 95% CI, 1.01-1.67).⁷⁰ Deaths due to cardiac disease were not significantly increased (15 and 13 per 10,000 woman-years in E/PT and placebo-treated groups, respectively). In the final analysis of the WHI E/PT trial, the HR was lower and less significant, 1.24 (95% CI 1.00-1.54). Significantly higher risk was observed only in the first year of E/PT treatment (HR 1.81, 95% CI, 1.09-3.01) and risk did not correlate with age at study entry, body mass index, presence of vasomotor flushes or night sweats, or aspirin or statin use. An excess risk of CHD was observed in E/PT-treated women who were > 20 years postmenopausal at the time of study entry or had higher baseline levels of LDL-cholesterol.⁷⁰

Do the results of the HERS and WHI trials differ from the observational studies because the intervention included progesterin? In the epidemiologic studies, ET was the dominant treatment and progesterin diminished some of the intermediate effects of ET on lipids and other heart disease risk factors. However, in the five epidemiological studies which provided information about ET and E/PT exposure, the average risk reduction was 39% (95% CI, 27-49%) with ET and 31% (95% CI, 13-45%) with E/PT.^{26,34,71,36}

Level I evidence indicates that HT is not indicated for the primary or secondary prevention of coronary artery disease events. Alternative health strategies and pharmaceutical agents with established value should be used for primary prevention of CHD. Women with established CHD are at high risk for MI and cardiac death and frequently do not receive adequate treatment for secondary prevention.³²

The WHI study results are relevant to long-term use of E/PT among women aged 50 to 79 years who are predominantly healthy and free from estrogen deficiency symptoms. Risks may vary with lower doses, different formulations and non-oral routes of HT administration.

(Editor's Note: Data from the recently stopped estrogen-only arm of the WHI suggest that addition of continuous prog -

estin does impact the risk-benefit ratio. When the data from the estrogen-only arm are published, additional changes in practice guidelines may be required.)

STROKE

The incidence of stroke among otherwise healthy postmenopausal women is approximately two per 1,000 per year, and approximately 75% of strokes are ischemic.^{30,37,38} In 29 different epidemiological studies, stroke endpoints and HT definitions were inconsistent and there was no conclusive evidence for a beneficial or harmful effect of HT on stroke risk.³⁵ The Nurses Health Study reported a trend toward increased risk with combined continuous E/PT. Only a small non-significant increase in risk was observed for ET (relative risk 1.18, 95% CI, 0.95-1.46), but for E/PT the risk was 1.45 fold higher (95% CI, 1.10-1.92) for any type of stroke, compared with never users.³⁷

Stroke risk associated with E/PT has now been addressed in two RCTs, HERS and WHI. In HERS and HERS II combined continuous E/PT was not associated with an increased risk for transient ischemic attack (TIA) (relative hazard (RH) 0.90, 95% CI, 0.84-1.43) or ischemic stroke (RH 1.18, 95% CI, 0.84-1.43), compared with placebo, but HERS lacked the necessary power to evaluate these small relative changes in risk.³⁸ Overall, the RH for any stroke or TIA was 1.09, a non-significant increase.¹¹

In the WHI study of E/PT, 151 women (1.8%) in the E/PT group and 107 (1.3%) in the placebo group had strokes,³⁹ 80% of which were ischemic. The hazard ratios were 1.44 (95% CI, 1.09-1.90) for ischemic stroke and 0.82 (95% CI, 0.43-1.56) for hemorrhagic stroke. There were 26 and 18 ischemic strokes per 10,000 woman-years in the E/PT and placebo groups, respectively.

Stroke risk with ET has also been addressed in two RCTs. One involving 664 postmenopausal women with a recent stroke or TIA found that ET (1 mg estradiol valerate per day) did not reduce the risk of subsequent stroke or mortality over the 2.8 years of follow-up.⁴⁰ Similarly, ESPRIT did not demonstrate an increased risk of stroke or TIA.³¹

Presently available data show that HT does not provide protection against stroke and may increase the risk of ischemic stroke. Little is known about the characteristics of the patients who are at greatest risk of stroke while using E/PT.

VENOUS THROMBOEMBOLISM (VTE)

VTE is a rare but important risk for women receiving HT. Data from epidemio-

logic studies, HERS, and WHI consistently demonstrate an increased risk of VTE events in postmenopausal women who use ET or E/PT.^{13,30,41} In five epidemiological studies published between 1992 and 1997 involving 592 cases of VTE of which 130 (22.0%) were in current HT users, the risk of VTE was increased by approximately two-fold (typical OR 2.3, 95% CI, 1.7-3.0).⁴²⁻⁴⁶ In the HERS trial the relative risk of VTE was similar in magnitude: 2.66 (95% CI, 1.4-5.0).⁴⁷ The excess risk was 3.9 per 1,000 woman-years and the number needed to treat to cause harm in one additional woman with established heart disease (average age 66.7 years) was 256

*“More than
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(95% CI, 157, 692). VTE is not confined to the first year of HT use, but risk declines from approximately four-fold in the first year to less than two-fold after the third year of use.^{13,42,45,46} In HERS II, the 2.7-year unblinded follow-up study of women with existing CHD receiving E/PT, VTE was not significantly increased (RH 1.40, 95% CI, 0.6-3.0).

The WHI study confirmed the magnitude and timing of the VTE risk estimates from previous studies. There were 34 and 16 VTE events per 10,000 woman-years in the E/PT and placebo groups, respectively, an increase that was significant after adjusting for multiple statistical testing (HR 2.11, adjusted 95% CI, 1.26-3.55). The relative hazard for pulmonary embolism (2.13) and deep venous thrombosis (2.07) were similar. VTE events decreased over time during the study (z for trend = -2.46, P = 0.014).

Continuing research on the prevalence

and effects of procoagulation factors and the genetics of VTE risk may identify screening procedures to reduce overall risk among women using HT. At present, routine screening of women for thrombophilia is not indicated prior to initiating HT. VTE risks may vary according to the route of administration of HT, since oral estrogens are associated with greater impact on coagulation factors than transdermal or vaginal routes of administration.⁷²

ENDOMETRIAL CANCER

Epidemiologic studies since 1975 have consistently shown that unopposed estrogen increases the risk of endometrial cancer among women having a uterus. Data from 30 case-control studies and seven cohort studies suggest that risk among ever users of ET is increased approximately 2.8-fold (95% CI, 2.6-3.0) than in never users.⁴⁸ Moreover, there is a significant trend toward increasing risk of endometrial cancer with increasing duration of ET; risk is 2.0-fold higher (95% CI, 1.8-2.2) with less than five years of use and 6.7-fold higher (95% CI, 5.9-7.6) with longer durations of ET. After discontinuation of ET, the relative risk remains elevated; risk is still 3.5 times higher (95% CI, 3.0, 4.0) for up to five years after treatment ends, and 2.5 times higher (95% CI, 1.9-3.2) five and more years after discontinuing ET. The ET-associated endometrial cancer risk is similar for different estrogen preparations and higher doses are associated with a small additional increase in risk.⁴⁸

Treatment with progestogens appears to reduce the risk of endometrial cancer associated with ET in a duration-dependent manner. Endometrial cancer risk is decreased with either cyclic or continuous E/PT. Cyclic regimens including more than 10 days of progestogen exposure per month appear to provide maximum protection. Morphological and biochemical studies suggest that shorter durations of cyclic progestogen treatment may not prevent development of endometrial hyperplasia. The risk of endometrial cancer associated with less than five years of continuous E/PT was 1.01 (95% CI, 0.76-1.35) and 0.86 (95% CI, 0.53-1.42) for five or more years of use.

Both the HERS and the WHI E/PT trials confirmed that continuous E/PT has no effect on risk for developing endometrial cancer. In the WHI trial, five and six cases of endometrial cancer were observed per 10,000 woman-years in the E/PT and placebo groups, respectively, yielding a small but significant decrease in risk (RH 0.83, adjusted 95% CI 0.29, 2.32).

HT AND BREAST CANCER

Estimates of HT-associated breast cancer

risks vary widely, mainly because studies involving fewer than 200 HT-exposed breast cancer cases are too small to estimate risk with precision. The WHO Collaborative Group report attempted to overcome the limitations of small sample size by combining data from 90% of the published epidemiological studies, which together included 52,705 women with breast cancer.⁴⁹ For current users of HT and those who stopped using HT one to four years before, breast cancer risk increased 2.3% per year of use, an effect comparable to that of delayed menopause (2.8% increase in risk per year of delay). For short-term HT use (one to four years), the increase in risk was not significant (1.05, 95% CI, 0.99-1.12). After five years of current use, risk increased significantly by 12% (RR 1.12). For current users of HT for five years or longer, the relative risk was 1.35 (95% CI, 1.21-1.49). Overall, the increase in breast cancer risk was most evident in women having a BMI < 25 kg/m² and risk of localized, but not metastatic, disease was increased. Within five years after discontinuing HT, the increased risk associated with HT use virtually disappeared.⁴⁹ Both the combined report and subsequent separate studies indicated that dose and type of estrogen did not affect breast cancer risk.⁴⁹⁻⁵¹

Combined estrogen-progestin therapy increases the point estimates for breast cancer risk compared with estrogen alone, but there were relatively few cases exposed to combined therapy in the collaborative analysis.⁴⁹ Several studies subsequent to the collaborative analysis include subjects with combined estrogen-progestin HT exposure. In the Breast Cancer Detection Demonstration Project (BCDDP), the per annum breast cancer risk was 1.01-fold higher (95% CI, 1.002, 1.03) with E/T alone and 1.08-fold higher (95% CI, 1.02, 1.06) with combined E/PT. Only 12 cases used a progestogen for 15 days or more per month, so this estimate reflects cyclic use of progestogens.⁵¹ Current and recent use of ET was associated with a nonsignificant RR of 1.2 (95% CI, 1.0-1.4), and similar use of E/PT was associated with a significant RR of 1.4 (95% CI, 1.1-1.8). In a case control study, the per annum relative risks calculated from the data for unopposed estrogen, cyclic combined estrogen-progestin and continuous combined estrogen-progestin were 1.015, 1.076, and 1.018, respectively.⁵⁰ Per five years of use the relative risk for developing breast cancer was 1.06 (95% CI, 0.97-1.15) for ET, 1.38 (95% CI, 1.13, 1.68) for cyclic progestin plus estrogen, and 1.08 (95% CI, 0.88, 1.35) for continuous combined estrogen-progestin. A recent multicenter, population-

based case-control study demonstrated a significantly increased odds ratio (OR) with five or more years of current use of continuous combined HT (1.54, 95% CI, 1.10-2.17) but no increased risk with either cyclic progestin HT (OR 1.07) or ET (OR 0.81). As with other studies,⁵² the increased risk dissipated very quickly after discontinuing therapy.⁵³ Most recently, a population-based case-control study that confirmed the increased risk associated with long-term therapy (> 5 years), found no difference regardless of whether the progestin component of HT was administered cyclically or continuously, and suggested an increase in lobular carcinoma as well as invasive ductal carcinoma.⁷³ The

“The usual reason for prescribing HT is the treatment of vasomotor symptoms.”

data remain inconclusive but suggest that cyclic and combined E/PT may present a slightly higher breast cancer risk than ET. In all of the studies, however, risk was minimal with less than five years' duration of use. Increased risk appears to be limited to current use of at least five years and recent users of long-term therapy.

A key analysis in the collaborative study showed that the breast cancer risk associated with current or recent HT use for five years or more and a positive family history for breast cancer was lower than the HT-associated risk with a negative family history.⁴⁹ A subsequent cohort study found a higher ratio of HT-associated breast cancer risk with a positive family history,⁵⁴ but the combined results of the cohort study and the collaborative analysis indicate that the relative risk of breast cancer risk associated with five years or more

of HT use currently or within five years was 1.13 (95% CI, 0.82, 1.57) with a positive family history and 1.32 (95% CI, 1.20, 1.46) with a negative family history of breast cancer. Therefore HT does not appear to further magnify the higher breast cancer risk associated with a family history of breast cancer.

During the three years of the HERS trial, breast cancer risk was not elevated. There were 34 and 25 new invasive breast cancer cases in the HT and placebo groups, respectively, a non-significant increase (relative hazard 1.38, 95% CI, 0.82, 2.31).⁴⁷ During the average 5.2 years of exposure during the WHI trial, there were 38 and 30 new invasive breast cancer cases per 10,000 woman-years in the HT and placebo groups. The relative hazard of 1.26 (95% CI, 1.00, 1.59), although not statistically significant, was associated with a highly significant trend analysis that demonstrated increasing risk with increasing duration of use.³⁰ Frequency of surveillance by mammography was equivalent in both WHI study groups.

To better understand the relationship between breast cancer and HT, the WHI performed a detailed analysis of the breast cancers that developed during the study and extended the mean follow-up period to 5.6 years. The unweighted hazard ratio (HR) was 1.24 for total breast cancer (95% CI, 1.02–1.50), 1.24 for invasive breast cancer (95% CI, 1.01–1.54), and 1.18 for in situ cancer (95% CI, 0.77–1.82). Invasive breast cancers were of similar histology and grade in HT and placebo groups, but HT was associated with slightly larger tumor size, 1.7 cm vs 1.5 cm (P = 0.4) and cancers in the HT group were more likely to be lymph node positive, 25.9% vs 15.8% (P = 0.3) (74,56). In addition, the WHI data suggest that women taking E/PT are more likely to require additional diagnostic studies for equivocal mammographic findings than non-HT users.

The invasive breast cancer risk with HT in both RCTs is small and similar in magnitude to the breast cancer risks indicated by the Collaborative analysis. Also, the timing of the risk was similar: breast cancer risk was the same in HT and placebo groups for four years in the WHI study, while in the Collaborative study, breast cancer was not significantly elevated until after five years of use.

The absolute effect (eight and 17 cases per 10,000 women per year in the WHI and HERS trials, respectively) is low and in the range of the increased breast cancer risk from two glasses of wine per day. The Collaborative analysis estimate of the absolute risk of breast cancers among users of estrogen plus progestin HT was based

on incidence rates intermediate between the United Kingdom and the United States. Among 1,000 non-HT users aged 50 years, 20 breast cancer cases would be diagnosed in 10 years. With five and 10 years of HT use, there would be two and six additional breast cancer cases, respectively. An absolute risk of this magnitude has public health significance, but for the average woman it is generally below the level which affects decisions about hormone replacement therapy. Moreover, most studies published to date suggest that breast cancer survival is not adversely affected, and may be improved, in women who were taking HT at the time of diagnosis.⁵⁵ The Million Women Study, in contrast, demonstrated an increased risk of fatal breast cancer in current users of HT (RR 1.22, 95% CI, 1.05-1.41) but not past users (RR 1.05, 95% CI, 0.85-1.29).⁷⁵

The increased risk of invasive breast cancer seen in the WHI is similar to that reported in prior studies. The WHI found that in situ breast cancer incidence was not significantly different among HT and placebo users. Breast cancer mortality tends to be lower in observational studies among patients who were HT users.⁵⁵ The mortality data that will continue to come from the WHI study may indicate whether the estrogen plus progestin HT-breast cancer link is causal or due to HT-mediated facilitation of early diagnosis. Our knowledge gap concerning the risks of ET should be answered when the estrogen-only arm of the WHI reports its data. A knowledge gap still exists regarding the safety of administering HT to symptomatic women who survive disease-free after treatment for localized breast cancer.

COLON CANCER

An important but as yet unproven benefit of long-term HT may be a reduction in the risk of colon cancer, an observation in numerous epidemiological studies. One possible biological rationale is a reduction in the concentrations of bile acids which are potentially tumor-promoting, a hypothesis associated with the lower risk among women who have been pregnant or taking HT. Another possibility is linked to the dominant estrogen receptor subtype in the colonic mucosa, which is ER β . Evidence has emerged that this subtype is significantly decreased in colonic tumors from females. The epidemiological evidence was summarized in a meta-analysis which included 25 epidemiological studies and distinguished between risk of colon cancer and risk of rectal cancer.⁵⁶ Rectal cancer incidence was not affected by HT use. For colon cancer, however, recent use of HT was associated with a 33% reduction in the

risk (RR 0.67, 95% CI, 0.59, 0.77). In a second meta-analysis, current users of HT demonstrated a 34% reduction in colon cancer (RR 0.66; 95% CI, 0.59-0.74).⁵⁷

This promising benefit was consistent with the WHI RCT results, in which there were 10 and 16 new colorectal cases per 10,000 woman-years in the estrogen-progestin HT and placebo groups, respectively. This small benefit of HT was not significant, however, after adjusting for multiple statistical testing (relative hazard 0.63, adjusted 95% CI 0.32, 1.24). Time trend analysis showed a benefit for colorectal cancer after three years of HT use.

More research is needed into the mechanisms by which estrogen with or without progestin might influence the development of colon cancer. Results might guide focused trials to evaluate whether the observed reduced incidence is due to hormone use or alternative actions.

EPITHELIAL OVARIAN CANCER

Epithelial ovarian cancer shares certain reproductive and hormonal risk factors with endometrial cancer: it is less common in parous women and in those who have used oral contraceptives or had an early menopause.^{58,59} Ovarian cancer incidence also is higher among well-educated women and those in the highest social classes who are most able to pay for HT.⁶⁰ One meta-analysis of 15 case-control studies found heterogeneous risk estimates and the summary odds ratio was not significant (OR 1.1, 95% CI, 0.9-1.3) (61). In a pooled analysis of data from four European case control studies, the ovarian cancer risk was 1.7-fold higher (95% CI, 1.3-2.3) for ever users of HT compared with never users.

In a Swedish case control study reported in 2002, epithelial ovarian cancer risk was increased with ever use of unopposed estrogen (adjusted OR 1.43, 95% CI, 1.02-2.00) or estrogen with sequential progestin (OR 1.54, 95% CI 1.15 - 2.05).⁶² Ever use of estrogen with continuous progestin, however, was not associated with increased risk (OR 1.02, 95% CI, 0.73-1.43). Another 2002 report of an analysis of ovarian cancer incidence during 19 years of follow-up in the Breast Cancer Detection Demonstration Project estimated that ovarian cancer risk was 1.6-fold higher (95% CI 1.2-2.0) in users of estrogen-only, but not increased in users of estrogen-progestin (adjusted RR = 1.1, 95% CI, 0.64-1.7).⁶³ Short-term use of ET for less than four years, or four to nine years, was associated with a small but nonsignificant increased risk. Increased duration of ET use for 10 or more years was associated with a significantly increased risk of ovarian cancer (RR 1.8, 95% CI, 1.1-3.0). Overall, the results of the

two 2002 epidemiologic studies, as well as an earlier prospective study of 944 fatal cancers,⁶⁴ are consistent in finding an increased risk with long term unopposed estrogen use but not when estrogen is combined with progestin. Ovarian cancer mortality, unlike breast cancer mortality, may be increased among users of ET, but the reported 1.5-fold higher risk (95% CI, 1.2, 2.0) among long-term ever users did not include exposure information after 1982.⁶⁴ Although epithelial ovarian cancer is an uncommon disease, the mortality ratio is high.

At the present time, it is uncertain whether the observed effects of HT on epithelial ovarian cancer reflect bias, chance, or reality. Further studies are needed involving current patterns of HT usage to determine whether ovarian cancer is an important risk factor with use of combined estrogen-progestin. Further studies on long-term ET and E/PT will need to address the impact of dose, duration, and prescription schedule.

SYMPTOMS AND SIDE EFFECTS DUE TO HT USE

Irregular or withdrawal bleeding with HT is a frequent reason for early discontinuation of treatment.⁶⁵ Factors in favor of continuation are those associated with less likelihood of bleeding: hysterectomy, an older age when initiating treatment, age greater than 60 years, use of continuous combined rather than sequential combined HT, and a sufficient dose of progestin in continuous combined HT.⁶⁶⁻⁶⁸ In a multicenter RCT involving 1,724 postmenopausal women, bleeding was reported in 15% of the estrogen-only cycles, 18% of the continuous combined HT cycles, and 74% of the sequential therapy cycles.⁶⁷ In ESPRIT, 208 of 373 women who had not had a hysterectomy had vaginal bleeding while taking estradiol valerate.³¹ In five RCTs involving continuous combined regimens, bleeding rates were approximately 35% at cycle two or three, 24% at cycle six and 16.5% (95% CI, 14.5, 18.9) at cycle 12. Overall, bleeding is least likely with continuous combined estrogen and progestin regimens. Breast pain was present at baseline in 4% of women in the PEPI trial. Compared with placebo treatment, breast symptoms were not worse with unopposed estrogen, but were approximately two-fold more likely with each of the three progestin formulations. For every 21 (95% CI, 12, 90) patients treated with progestin formulations for three years, there would be one more with worse breast symptoms than in 21 placebo-treated women.¹

Musculoskeletal symptoms were commonly reported by subjects before treat-

ment in the PEPi trial, including aches and pains (48%), joint pain (44%), muscle stiffness (42%), and skull and neck aches (34%).¹ This group of symptoms was significantly improved in the regimens combining conjugated estrogens with cyclic or continuous medroxyprogesterone acetate. The frequency of headache was not significantly changed during treatment. At baseline 32% of the women in the PEPi trial reported concerns about perceived weight gain with hormonal therapy. The proportion reporting this perception was decreased in the hormone treatment groups at 12 and 36 months, and the reduction was significant in the CEE and continuous MPA group (odds ratio 0.61, 95% CI, 0.41, 0.91).¹

The WHI study has not yet reported on symptomatic side effects of HT use. HERS reported that standard HT dosages in elderly women were associated with increased complaints of vaginal discharge, genital irritation, uterine bleeding, and breast symptoms. Uterine bleeding occurred in 31% and spotting in another 33% of the HT group during the first year of the study. These numbers reduced to 11% and 20%, respectively, during the fourth year. Placebo treatment was associated with rates of 2% and 13% during year one, and 2.5% and 6% during year four. There was no difference between the HT and placebo groups in reported weight gain.²

SUMMARY AND CONCLUSIONS

- Hot flushes occur in over 50% of women entering the menopause and the frequency declines to 30% after three years. Symptoms may persist, however, in up to 16% of women at 67 years of age.
- The usual reason for prescribing HT is the treatment of vasomotor symptoms. The average patient is a woman aged 45 to 60 years, and the most common duration of use is less than three years.
- Estrogen with or without progestogen is an effective treatment for urogenital atrophy, but may worsen urinary incontinence.
- Estrogen and progestogen reduce risk of osteoporotic fractures of the hip, vertebrae, and other sites, but the effect on hip fracture is small, and HT treatment is not warranted solely for fracture prevention.
- Although estrogen was associated with a 34% reduction in the risk of senile dementia in epidemiological studies, the WHIMS failed to corroborate these observations.
- HT is not indicated for the primary or secondary prevention of coronary artery

“ET and E/PT are associated with side effects that include breast tenderness, vaginal discharge, and uterine bleeding.”

disease events. Alternative health strategies and pharmaceutical agents with established value should be used for primary prevention of coronary heart disease.

- Risk of venous thromboembolism is increased among women using E/PT and declines during continuing use. Route of administration may affect the magnitude of risk.
- E/PT treatment has a small but significant effect on breast cancer risk equivalent to eight new cases per annum per 10,000 women. The increased risk is seen after five years of current use and disappears several years after discontinuing therapy.
- Epidemiological studies suggest that there is a small but significant increased risk of epithelial ovarian cancer with unopposed estrogen use that is not observed when estrogen is combined with progestin. The effect is significant in women who take ET for 10 or more years.
- ET and E/PT are associated with side effects that include breast tenderness, vaginal discharge, and uterine bleeding. Weight gain is not more common in hormone users.
- The current indications for ET and E/PT include the treatment of moderate to severe vasomotor symptoms, the treatment of vulvar and vaginal atrophy, and the prevention of osteoporosis.

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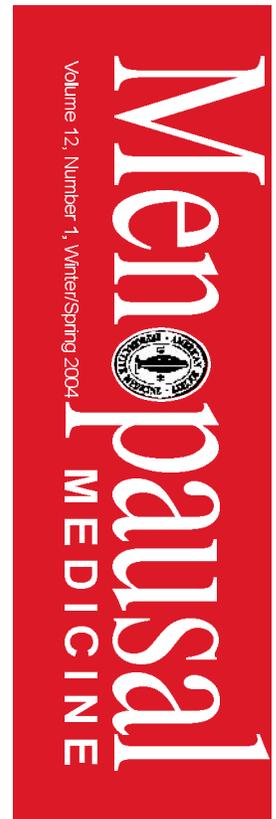
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This report was developed under the direction of the Practice Committee of the American Society for Reproductive Medicine as a service to its members and other practicing clinicians. While this document reflects appropriate management of a problem encountered in the practice of reproductive medicine, it is not intended to be the only approved standard of practice or to dictate an exclusive course of treatment. Other plans of management may be appropriate, taking into account the needs of the individual patient, available resources, and institutional or clinical practice limitations. The Practice Committee of the American Society for Reproductive Medicine and the Board of Directors of the American Society for Reproductive Medicine have approved this report in September 2003.



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