

American Society for Reproductive Medicine Menopausal MEDICINE

Volume 7, Number 3, Fall 1999

FOR CLINICIANS WHO PROVIDE CARE FOR WOMEN

Rationale for Ovarian Conservation in Women



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INTRODUCTION

Medical science now identifies many serious life-threatening diseases resulting from long-term estrogen and androgen deficiency. The practice of removing normal ovaries in women over 45 originated during a period when there was little knowledge regarding direct relationships between sex hormones and diseases. It is time to re-evaluate the belief that the 45-year-old ovary is either a useless organ or an easily replaceable organ that should be "removed at sight."

Rather than offer a rationale for ovarian conservation in women, a better question is, "Why, without good reason, completely remove the source of beneficial ovarian hormones and thereby increase the risk of many serious life-threatening diseases and hormone deficiency problems?"

OVARIAN HORMONE PRODUCTION: BUILT-IN PROTECTION FROM MANY DISEASES

It is well established that estrogen deficiency is associated with cardiovascular disease and coronary artery atherosclerosis,¹⁻¹³ osteoporosis,¹⁴⁻¹⁶ cognitive functioning decline,¹⁷⁻²³ senile dementia,²⁴⁻²⁸ mood disorders/depression,²⁹⁻³⁴ urogenital problems,^{35,36} sexual function,³⁷⁻³⁹ and

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vasomotor instability.⁴⁰ Androgen deficiency affects bone loss,⁴⁵⁻⁴⁹ libido,³⁷⁻³⁹ muscular preservation, fat distribution,^{51,52} and a woman's sense of well-being, including energy and appetite. The burden of proof for removal of ovaries rests on a clear demonstration that the advantages of removal are greater than the problems associated with their removal. The data are heavily in favor of ovarian preservation for the pre-, peri- and early postmenopausal age groups (through age 55) and very strong for those over 55 years of age.

RISK-BENEFIT ANALYSIS: WHAT CONDITIONS MERIT OOPHORECTOMY?

There are few if any conditions, except ovarian cancer, where removal of normal ovaries has been shown to have a greater benefit than risk profile.

One area for ponder (and need for further studies and more options) involves surgical management of chronic pelvic pain. Reports vary greatly in the success and failure rates of hysterectomy (with or without oophorectomy) for relief of pain, but clearly surgical intervention does relieve pain in some women. There are a few retrospective studies reporting lower re-operation rates and a higher percentage of pain relief when ovaries were removed in patients with symptomatic endometriosis. All of these studies failed to follow patients for compliance with estrogen

FROM THE EDITOR

David F. Archer, M.D.

Dr. Donna Shoupe makes a strong case for ovarian conservation in women over the age of 45 in her well organized and extensively referenced paper. The points she makes are valid. Rates of elective oophorectomy are between 50% and 66% in women between the ages of 40 to 64 years. It is estimated that 1,000 ovarian cancers could be prevented by prophylactic oophorectomy. In order for this reduction in ovarian cancer occurrence, 300,000 bilateral oophorectomies would have to be performed [ACOG Practice Bulletin, Number 7, September 1999]. Physicians should seriously consider the positive benefits of ovarian conservation for patients at any age.

Dr. Johanna S. M. Archer places in juxtaposition three elements to support the effect of estrogen on the central nervous system. These are the clinical occurrence of depression or mood changes, the neuroendocrinologic effects of estrogen on neuro-transmitters, and clinical trials that evaluate quality of life and psychological testing. It is apparent that estrogen has multiple positive effects on CNS function and could be used for treatment in some instances.

Dr. Christine L. Cook contrasts the effects of transdermal estrogen and estrogen plus progestin vs. oral estrogen and progestogens on a variety of clinical outcomes, biochemical parameters, and CNS function. Transdermal delivery of both estrogen and progestins is now a reality. Physicians should take notice of this route of administration of HRT for their patients.

Menopausal Medicine

A Newsletter of the
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The ASRM is pleased to acknowledge the generous
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replacement or report long-term changes in bone density, hypertension, heart disease, depression, sexual problems, or dementia.

Removal of ovaries in women under the age of 55 increases the risk of cardiovascular disease and osteoporosis by two to seven fold as well as a host of other conditions detailed below. In many cases, the benefit of assuring no more surgeries directed at ovaries is traded for future angiographic procedures or hip replacement surgeries.

As women reach 60 and older, their ovaries often offer them a limited protection from cardiovascular disease and osteoporosis. The protection from cardiovascular disease is a result of small amounts of direct ovarian estrogen production⁵³⁻⁵⁷ plus peripheral conversion of large amounts of ovarian androgens to estrogens.^{58,59} The greatest impact of removal of ovaries in the >60 year olds, however, is the loss of androgen production.^{53-57, 60-62} Ovarian androgens importantly stimulate bone and muscle growth⁴⁵⁻⁵⁰ and contribute to many of the psychological benefits discussed below.

THE BEST REBUTTAL ARGUMENT

The accumulating data showing significant beneficial impacts of estrogen or hormonal replacement therapy (ERT or HRT) for menopausal women may influence clinicians to assume that these benefits are "a given" and thus the ovary is easily replaced. There are at least five major problems with this rationale:

1. The "one dose fits all" for hormone replacement therapy doesn't work. There are many factors that also affect the HRT dose requirement. The HRT dose needed for the naturally, early menopausal 53-year-old, who is moderately overweight and taking calcium supplementation, is very different from the 47-year-old slender smoker who just had a bilateral oophorectomy. A recent study documented that low doses of continuous estrogen therapy (i.e., .3 mg conjugated equine estrogen) plus adequate calcium and vitamin D in >65 yrs old women is bone protective.

It is extremely difficult for even the most experienced clinician to determine for each patient, the dose, route, and combination therapy that provides adequate protection from the changes associated with oophorectomy and the loss of ovarian estrogens and androgens. Most

prospective studies show short-term effects of one or two doses of ERT/HRT on one organ system, most commonly on bone loss, in women generally in their 50s. Most cross-sectional studies show general trends of a variety of ERT doses on several organ systems in older postmenopausal women. The optimal dose for different age groups is not well understood, especially in women less than 50 or over 70.

2. The effect of oophorectomy for some women is very adverse. These are the patients that complain of "feeling lousy" despite many attempts at taking ERT. They complain bitterly of not feeling well, of depression, or of losing their sexual desire. A sudden loss of the usual "mix" of sex hormones can dramatically and adversely affect certain women. No one has yet figured out a way to determine pre-operatively which women will be so affected.

3. Notwithstanding the known benefits of ERT, compliance with ERT is low. While educational efforts may be successful in increasing compliance, studies continue to show that long-term use ranges from 2% to 46% in surgical menopausal patients. While this is better than the 2% to 20%⁶⁹ long-term use reported in natural menopausal women, the ill effects of oophorectomy in an aging, non-compliant population takes a toll.

This compliance issue is a better argument for premenopausal or perimenopausal (i.e., under 52 years of age) women as adding years of pill taking is expensive, bothersome, makes little sense, and (worse) may not happen. But even in older patients, ovarian hormone production is often quite high up to age 55 and as discussed later, can be substantial in some. Missing a week of hormone replacement therapy in a naturally menopausal woman is of less concern than in a surgically menopausal woman.

4. Is there any other organ in the body where clinicians would argue for removal of a functioning, healthy organ, with the rationale that the patient can take a pill every day for the rest of her life? Having to take thyroid medication for 20 years is as easy as taking ERT, but justifying removal of a normal thyroid with this excuse is not practiced. In pre- or perimenopausal women, even ignoring the cost and inconvenience of buying the medication, these often otherwise healthy women are suddenly burdened with taking

a medication every day for the sole purpose of replacing hormones that are now absent because of the surgery just performed. Table 1 lists the documented changes that occur within months unless appropriate hormone replacement is initiated and continued. The common statement that “you don’t need your ovaries so we’ll just remove them” should be replaced with “your ovaries protect you from many pathologies, they are valuable, and are not easily replaced.” Keeping protective androgens and small amounts of estrogen has value; keeping ovaries has value.

5. While many surgeons are convinced that premenopausal ovaries should be spared, they continue to believe that postmenopausal ovaries are not valuable, or easily replaced. The older she is, the more likely she is to discontinue HRT. Data from a California health maintenance group showed the highest rates of HRT/ERT use is among 50-year-olds (45%). By age 70, the percentage of users is under 15%.

THE POSTMENOPAUSAL OVARY: MANY VALUABLE FUNCTIONS

In natural menopause, the decline of ovarian function is not a sudden event. The decline in function during natural peri- and postmenopause is a gradual process that begins as early as age 35 when the ovary begins to shrink in size.^{56-57,63} The average age of menopause is 52 years in non-smoking, non-obese, non-hysterectomized women. During the first four years after the menopause, many ovaries continue to secrete estrogen in amounts only slightly below levels found in the early follicular phase of the menstrual cycle. Removal of ovaries in women up to age 56 often results in measurable decreases in serum estrogen and testosterone levels.^{54,55,64}

In women over age 56, ovarian estrogen secretion is generally from 10 to 15 µg/day.^{54,64} About 10% of postmenopausal ovaries secrete up to 20 µg/day of estradiol.^{55,56,61,68} The small amounts of estrogen produced by postmenopausal ovaries may be significant and offer more or less limited protection from heart disease and other estrogen deficiency diseases. Stromal tissues from ovaries in women who are up to 30 years postmenopausal have been shown to secrete estradiol and androstenedione in vitro.⁶¹

Transient surges in estradiol serum levels occasionally occur in postmeno-

pausal women.^{55-57,65,68} These elevations may reflect activity in a residual follicle.

The 50% fall in circulating androgens, mainly from a fall in androstenedione production from the ovary, generally precedes the menopause.⁶⁸ After the menopause, there is very little change, if any, in testosterone levels. In most postmenopausal women, a major source of circulating estrogens is from the peripheral aromatization of androgens.⁶⁸ As a result, oophorectomized women have significantly lower estrogen levels, as well as lower testosterone and androstenedione levels than naturally postmenopausal women.

In postmenopausal years, 50% of circulating testosterone is produced by the postmenopausal ovary as compared to only 25% in the reproductive years, while 10% is secreted by the adrenal gland, and 40% is derived from peripheral conversion. While most postmenopausal women have levels of circulating testosterone well below the mean for young women, there are postmenopausal women with levels above that mean (Table 2).⁶⁸

DOCUMENTED ADVERSE EFFECTS OF OOPHORECTOMY

Studies that separate surgical menopause from natural menopause report higher incidence and severity of estrogen-deficiency related problems in the surgical menopausal women. Oophorectomy in rats results in brains that are deficient in acetylcholine, a hallmark of Alzheimer’s disease.²⁰ In primate colonies, oophorectomy results in accelerated atherosclerosis which, only in part, is prevented by estrogen treatment.^{12,66}

1. Influence of bilateral oophorectomy on lipids; Many reports demonstrate an adverse effect of oophorectomy on lipids.^{13,67} In one study where surgical menopausal women were age- and body-matched with controls, triglycerides, LDL-C, Apo B levels, and the index of arteriosclerosis were all significantly higher in the surgical menopause group, while HDL-cholesterol was lower (Figure 3). The authors suggest that oophorectomized patients should have careful follow-up of lipids.

2. Influence of surgical menopause on cardiovascular disease (CVD); Up until at least age 55, premenopausal status protects

Table 1: Changes Documented Following Oophorectomy

1. Increase in cardiovascular disease, adverse effect on lipids, clotting parameters
2. Increase in osteoporosis, hip fracture
3. Decline in cognitive thought, memory
4. Accelerated collagen, skin loss, wrinkling
5. Higher rates of depression
6. Onset of mood changes/problems
7. Decline in sexual function, libido
8. More severe, prolonged hot flashes
9. More severe urogenital atrophy
10. Shift in waist/hip ratio

women from cardiovascular disease (Figure 4). Wuest and colleagues reported that women were protected from cardiovascular disease until the menopause; thereafter the incidence increased, and by 10 years after menopause approached the incidence found in men. The clear exception to this was oophorectomized women, who, within a very short period of time after oophorectomy, developed the same risk as men their own age.¹¹ The finding of an accelerated incidence of atherosclerosis, particularly myocardial infarction, in women who have undergone surgical oophorectomy has been well documented since this first report.¹⁻¹³ The Nurses’ Health Study reported 2.5 higher rates of CVD in oophorectomized women compared to controls.⁴⁶

3. Osteoporosis and hip fracture and surgical menopause; Later natural menopause is associated with a protective effect on bone mineral density (BMD).¹⁶ Women whose ovaries have been removed are more likely to have osteoporosis compared with age matched women without oophorectomy.¹⁶ Addition of testosterone to ERT results in increased urinary markers of bone formation and greater increases in BMD compared to ERT alone.^{49,50} These studies suggest that the lowered level of androgens in surgical menopausal women put these women at higher risk for these problems. One of the highest risk groups for osteoporosis and hip fracture is

Table 2: Common Hormonal Levels in Women

| | Reproductive Age | Post-Oophorectomy | Natural Menopause |
|-----------------------|------------------|-------------------|-------------------|
| Estradiol pg/mL | 35-500 | 0-15 | 4-20 |
| Estrona pg/mL | 20-200 | 25 | 30 |
| Androstenedione ng/ml | 150 | 70-90 | 80-90 |
| Testosterone ng/dL | 20-60 | 11 | 23 |

women who have had bilateral oophorectomy.¹⁴

4. Cognitive changes after oophorectomy; Evidence is accumulating that estrogen affects central nervous system function and that estrogen deficiency contributes to a deterioration of cognitive functioning.¹⁷⁻²³ Significant changes in cognitive thought within a few weeks of oophorectomy in perimenopausal women are well documented. Treatment with estrogen or androgen, or preservation of ovaries in women undergoing hysterectomy was associated with no change in cognitive ability.^{17,23} A similar study also supported the concept that hot flushes (and ovarian hormone loss) are associated with neuronal loss, as there was a significant association between the decline of cognitive function and the severity of hot flushes.⁷⁰

5. Links between estrogen deficiency, memory loss, and Alzheimer's disease; Sex steroids profoundly affect the concentration of neurotransmitters, affecting mood and mental performance.²⁸ There is wide-spread distribution of estrogen receptors within the brain.^{19,71} Estrogen acts as a neurotrophic growth factor; addition of estrogen to in vitro cultures of brain cells prolongs their survival.²²

There is compelling evidence that estrogen deficiency is associated with Alzheimer's disease. Women who experience myocardial infarction, considered an expression of estrogen deficiency, are five times more likely to develop dementia.^{27,71} There are multiple lines of research suggesting that estrogen stimulates many neurotropic factors in the CNS including nerve growth factor.²⁰

6. Estrogen deficiency and collagen loss; It has been shown that skin collagen and thickness decrease proportionally with time after the menopause.⁴¹ In untreated, mostly surgically menopausal women average age 51, a 30% loss of thigh skin collagen content within five to eight years after oophorectomy was documented.⁴¹

7. Estrogen deficiency and mood and depression; Endogenous opioid activity is low in oophorectomized women. Restoration is seen after three weeks of estrogen or estrogen plus progesterin therapy.³⁰

There is growing evidence that the risk of depression is higher in surgically menopausal women compared to naturally menopausal women. The deficiency of serotonin is thought to be one important causal factor in depression. A study of

2,500 middle-aged women in Massachusetts who had undergone surgical menopause showed them to have higher and clinically significant depression scores compared with women undergoing a natural menopause.^{32,33} The relationship between estrogen, brain function, and mood is an important reason not to accelerate the age of menopause or make it more severe.

8. Severe climacteric symptoms after surgical menopause; Women with surgically induced menopause tend to have a high incidence of hot flushes for the first year postovariectomy, compared to women undergoing natural menopause.^{73,76}

9. Adverse changes in sexuality after surgical menopause; There is now compelling evidence that sexual motivation is dependent on androgens. Additionally, androgens may also impact sexual desire and sensation.³⁹ A significant negative effect of oophorectomy on sexual function and arousal is documented in otherwise healthy women within weeks of surgery for benign disease. Similar changes did not occur in women with hysterectomy only or in those with oophorectomy treated with ERT. Patients receiving a combined estrogen-androgen intramuscular therapy reported higher levels of sexual desire and arousal and greater frequency of sexual fantasies compared to those treated with estrogen alone following surgery.³⁷⁻³⁹ Additionally, the frequency of coitus and orgasm was significantly greatest in patients receiving testosterone and estradiol.

OVARIAN CANCER RISK

The major chronic diseases that threaten women's health do not include ovarian cancer. A 50-year-old woman, not on ERT, has a lifetime probability of 46% and 31% of developing and dying from heart disease, 15% and 3% of suffering and dying from a hip fracture, 10% and 3% of developing and dying from breast cancer, and a 2.6% and 0.3% probability of developing and dying from endometrial cancer.⁷⁴ Her chance of dying from ovarian cancer is less than 1%.

CONCLUSION

It is difficult not to acknowledge that a premature, abrupt, and severe surgical menopause may have serious adverse consequences on health and well-being. It is difficult not to appreciate that ovaries protect from osteoporosis, muscle loss, loss of libido, and mood changes. By leaving

the ovaries there is often a natural base of androgens and estrogens, making the burden of choosing the right ERT regimen easier.

Make it easy for the doctor and the patient for the future; leave the ovaries! Preservation of the uterus and/or careful use of surgical techniques directed at leaving optimum blood supply to the ovaries also deserve consideration. It's now time for the ovary to have full recognition for the significant health benefits that ovarian hormones provide for women of all ages.

The author has revealed the following potential conflict of interest: Research/Consultant/Speaker for Parke-Davis, Organon, Wyeth-Ayerst, RPR, Berlex, Solvay, and Merck.

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Estrogen and Mood Change via CNS Activity



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INTRODUCTION

Front page stories about depression have surfaced lately in the popular press.^{1,2} All have grim predictions of the increasing prevalence and associated morbidity and mortality of depressive illnesses; one even going so far as to label depression a "public health crisis."² Currently depression is ranked as the world's fourth most devastating illness by the World Health Organization. There are projections that by 2020, depression will have climbed to second place behind heart disease.²

The prevalence of both major as well as chronic milder depressive conditions (dysthymia) has been consistently higher in women than in men. These findings cross cultural, ethnic, socioeconomic, and geographical boundaries.³ The National

Comorbidity Survey reported lifetime prevalence rates of major depression at 21% in women compared to 13% in men, and dysthymia rates of 8% in women compared to 5% in men.³ These gender differences occur only after the onset of puberty and persist until the age of 55.³

Recent advances in studies of brain function in both males and females have shown that the brain is a sexual organ.⁴ The brain responds differently in men than in women to a variety of stimuli. New technologies have allowed researchers to map out gender differences in the central nervous system (CNS). Gonadal hormones not only exert “organizational effects” during prenatal life to differentiate the brain according to gender, but also “activational effects” during adult life which support this gender differentiation.⁵ Gonadal steroids are among the most powerful peripherally generated biological signals in the CNS, affecting neurotransmitter synthesis, release and reuptake, as well as enzymatic inactivation and receptor density.⁶⁻⁹ Gonadal steroids not only impact through the classical nuclear receptor and resultant protein synthesis (enzymes, neurotropic growth factors, neurotransmitters, and neurotransmitter receptors) but also through direct membrane-mediated alterations.^{10,11} Neurobiologic changes in the central nervous system result in psychiatric disorders such as depression.¹²

The fluctuating levels of sex hormones seen during a woman’s menarchal life have been studied as a possible cause of a woman’s increased susceptibility to dysphoria.¹³ Three life stages have been identified that contain an increased risk of depression: premenstrual, postpartum, and perimenopausal,¹³ though there is still debate about an increased incidence of depression occurring during the menopause.¹⁴ This review will address the role of ovarian steroids, specifically estrogen, with regard to the pathophysiology and treatment of depression in the peri- and postmenopausal woman.

DEPRESSION IN THE CLIMACTERIC

Involuntary melancholia was included in the “Diagnostic and Statistical Manual” published by the American Psychiatric Association in 1968, but it was removed from the successive editions as clinical studies failed to show a consistently higher rate of depression in postmenopausal

women.⁶ Earlier reports evaluated only those women who attended menopause clinics and therefore were considered a self-selected population.¹⁵ Of women who seek medical advice for menopausal symptoms, 79% have physical complaints and 65% have depressive symptomatology.¹⁶ Several community-based studies found no evidence of an increased rate of depressed mood and clinically defined depression, while other cross-sectional community-based reports disagreed, reporting higher prevalence rates of clinically defined depression, 16% to 20% (which is double the point prevalence rate of 9%) during the climacteric.¹⁷

It appears that the rate of change of hormonal levels rather than the absolute value might be more important to the development of depression. Women who underwent a surgical menopause, thus experiencing a more abrupt drop in ovarian steroid serum levels, have been shown to have more severe psychological symptomatology than those undergoing a natural menopause.¹⁸ Women whose perimenopausal stage lasts longer than two years also have a greater incidence of depression.¹⁸ Changes in hormonal levels occur during the perimenopausal years, usually from 48 to 53 years of age. As many as 80% of these women develop mood disturbances that could not be solely attributed to vasomotor symptoms, such as hot flashes, night sweats, and insomnia.^{12,19}

Disagreement still exists as to the occurrence of a specific menopausal related depression. However, most researchers appear to agree that if such a disorder exists, it will occur more frequently in women who have a history of depression or premenstrual or postpartum mood symptoms.^{18,20}

NEUROENDOCRINOLOGY OF DEPRESSION

Estrogen receptors have been found in areas of the brain that are involved in emotion including the cerebral cortex, hypothalamus, hippocampus, amygdala, and limbic forebrain.¹⁵ Studies have shown that the limbic system, hypothalamus, g-aminobutyric acid (GABA) receptors, dopamine, serotonin (5-hydroxytryptamine of 5-HT), cholinergic, glutamergic, and opiate systems are all sexually dimorphic.²¹ All of these CNS neuroendocrine functions have been implicated in the manifestation of the depressive

state. One prominent neurologist/psychiatrist, Mark George, refers to depression as “depressions” to further delineate the numerous different biological pathophysiology basis and clinical appearances of this disease.¹

SEROTONIN AND ESTROGEN

The serotonergic system plays a substantial role in behaviors that are disturbed in the affective disorders, including mood, sleep, sexual activity, appetite, and cognitive ability.²² Serotonin is a component in the development of depression, but whether this neurotransmitter is the key player is still being determined.²² There are numerous studies involving both animals and humans investigating the role of the serotonergic system in depression. Lowering the dietary availability of tryptophan (the precursor of serotonin) in asymptomatic men will result in decreased plasma tryptophan and significant mood reduction.²³ Decreases in brain 5-HT concentrations can precipitate depression in recovered depressed patients.²² Metachlorophenylpiperazine (m-CPP), a serotonin agonist, can elevate mood in normal patients.²² Also, effective treatments for depression, specifically the selective serotonin reuptake inhibitors (SSRIs), have been found to enhance CNS serotonergic activity.²²

Basic animal investigations have shown numerous effects of estrogen on 5-HT synthesis, release, reuptake, and catabolism, with most aspects of central monoamine metabolism being modulated by sex hormones.^{24,25} Estradiol (E2) administered to ovariectomized rats significantly increased the density of 5-HT_{2A} binding sites in the anterior frontal, anterior cingulate, olfactory tubercle, piriform cortex, nucleus accumbens, and lateral dorsal raphe nucleus of the brain.²⁶ These areas in the CNS are involved in control of mood, emotion, and behavior.²⁶ Administration of 17 β -E2 induced a significant increase in 5-HT uptake in the frontal cortex and hypothalamus of ovariectomized rats.²⁷ This up-regulation mimicked the pharmacological activity of the tricyclic antidepressants.²⁷ Further studies with ovariectomized rats have shown that a recognized antidepressant mechanism of action, the reduction of 5-HT_{2A} receptor density, is not induced by chronic treatment with the antidepressant imipramine unless estrogen is also present.²⁸ The expression of the gene coding

for tryptophan hydroxylase, the rate limiting enzyme in 5-HT synthesis, was significantly increased in the presence of estrogen in ovariectomized rhesus macaques.²⁹

In women of reproductive age, there is a positive correlation between serum E2 levels and blood 5-HT concentrations.³⁰ Blood 5-HT levels are decreased in postmenopausal women when compared to premenopausal women.³⁰ When oral E2 was administered to these menopausal women, blood levels of 5-HT increased to levels comparable with the premenopausal state.³⁰ Postmenopausal women with and without estrogen replacement therapy (ERT) were evaluated for their response to m-CPP by measuring prolactin levels.³¹ Women receiving ERT had an increased prolactin response with m-CPP compared to women not taking ERT, indicating that ERT had enhanced central serotonergic activity.³¹ ERT also causes tryptophan, the precursor of serotonin, to be displaced from its binding sites to plasma albumin such that it increases the amount of free tryptophan available to the CNS.¹⁶

NEUROTRANSMITTERS AND ESTROGEN

Estrogen has effects on other neurotransmitters and neuromodulators, including the catecholaminergic, GABA, opioid, dopaminergic, and β adrenergic systems that are also altered in affective disorders (Table 1).^{10,32} Low levels of catecholamines, such as norepinephrine, are considered to be important in precipitating a depressive event.^{6,10} Several antidepressant medications all share the ability to block the reuptake of norepinephrine and thus increase the concentration of this catecholamine in the CNS.¹⁰ Estrogen has an overall stimulatory effect on norepinephrine through several mechanisms. Estradiol metabolites competitively inhibit the enzymatic inactivation of norepinephrine by catechol-o-methyl transferase (CoMT).³³ Monoamine oxidase (MAO) is

known to degrade 5-HT and norepinephrine in the neuron. Estrogen has been shown to reduce MAO activity resulting in higher levels of both catecholamines and 5-HT in the CNS.^{15,33} Thus estrogen mimics the actions of MAO inhibitors, a well-known class of antidepressants.²² MAO activity increases after menopause, resulting in plasma MAO levels in non-depressed premenopausal women that are approximately 75% lower than levels found in non-depressed postmenopausal women.³³ Elevated levels of plasma MAO activity in depressed women have been shown to be significantly reduced by the addition of ERT.³³

Estrogen also increases binding of GABA agonists and the upregulation of GABA receptors.³⁴ Drugs that enhance GABA function have been shown to alleviate depressive symptoms.¹⁰ Endogenous opioid activity is minimal in postmenopausal women but can be restored by ERT, so that the elevated mood seen in postmenopausal women receiving ERT can also be due to hypothalamic opiate activation and β -endorphin production.^{32,35} Estrogen also affects the dopaminergic system in a contradictory fashion depending on the type and location of the dopamine receptors.¹⁰ Estrogen alters the sensitivity of presynaptic dopamine autoreceptors in the substantia nigra and increases the number of postsynaptic dopaminergic binding sites in the striatum, resulting in an augmentation of the dopaminergic system.^{6,36} Other studies have shown that estrogen can have an inhibitory effect on dopamine activity, specifically D2 receptors in the anterior pituitary.^{7,10,34} In ovariectomized rats, a reduction in β -adrenergic receptors after long-term treatment with E2 was found.⁸ This is the only result that is common to several forms of antidepressant therapy, including electroconvulsive shock, MAO inhibitors, and atypical and tricyclic antidepressants.⁸

CLINICAL STUDIES UTILIZING ERT

In 1932, the first report of the antidepressant nature of estrogen in perimenopausal women was published.³⁶ Over 60 years later, there remains no clear agreement as to the role of estrogen in the treatment of depression. A meta-analysis of 111 articles published in 1995 on psychological symptoms of menopausal women receiving hormone replacement therapy (HRT) concluded that there was no apparent positive correlation between HRT and psychological improvement.³⁷ The authors also reported that few studies controlled for social stresses, vasomotor symptomatology, or placebo effect.³⁷ In addition, both standardized and non-standardized psychological tests were employed.³⁷ A meta-analysis performed two years later of 26 published studies evaluating the use of HRT and ERT on depressed mood found that ERT exerted a moderate to large effect on mood, while the addition of progesterone dampened the positive impact of estrogen.³⁸ In addition, the authors point out that the positive effects on depressive symptomatology by estrogen may not be apparent until after three months of treatment.³⁸

Several of these studies were flawed by numerous confounding variables. The designation of peri- and postmenopausal status in these women was not consistent across these studies, with some researchers evaluating serum hormone levels and others determining patient status by history.³⁸ In addition, plasma estrogen levels are variable during the perimenopausal transition with normal, low, and even high estrogen levels reported.²⁴ The designation of a woman as peri- or postmenopausal thus does not ensure a hypoestrogenic condition. There is also individual variation in diffusion rates across the blood-brain barrier for the sex steroids, such that it is difficult to extrapolate serum estrogen levels to those present in the CNS.¹¹ Therefore, it has been suggested that the patient can be used only as "her own best bioassay."¹¹

Researchers have used several psychological tests to measure depressed mood in women, including the Beck Depression Inventory and the Hamilton Rating Scale, which might not be appropriate in peri- and postmenopausal women. The Women's Health Questionnaire has been proposed as a more applicable test in this group of women, because it assesses mood and controls for somatic com-

Table 1: Alterations in Neurotransmitters in Depression and Estrogen Effects on Central Neurotransmitter Levels

| Depression | Estrogen |
|---------------------------------|---------------------------------|
| ↓ Norepinephrine | ↑ Norepinephrine |
| ↓ GABA | ↑ GABA |
| ↓ Opioid | ↑ Opioid |
| ↓↑ Dopamine | ↑↓ Dopamine |
| ↑ β -Adrenergic receptors | ↓ β -Adrenergic receptors |
| ↑ MAO | ↓ MAO |

GABA: γ -aminobutyric acid
MAO: Monoamine oxidase

plaints, vasomotor symptoms, and sleep disturbances.³⁹

Several well-designed studies by Barbara Sherwin showed that ERT enhances mood in postmenopausal women. In a prospective crossover study, healthy non-depressed premenopausal women underwent psychological testing prior to total abdominal hysterectomy (TAH) and bilateral salpingo-oophorectomy (BSO) for benign disease.¹⁵ They were then placed on monthly intramuscular injections of either estrogen, androgen, estrogen-androgen, or placebo for three months.¹⁵ During the fourth month, all participants received placebo before crossing over to a new treatment.¹⁵ For both treatment stages, women who received placebo had higher depression scores when compared to the women receiving any of the hormone preparations.¹⁵

Women in the perimenopausal period, determined by history and endometrial biopsy, were placed on oral conjugated equine estrogen (CEE) at 0.625 or 1.25 mg with placebo or with 5 mg medroxyprogesterone acetate (MPA).⁴⁰ All four groups reported heightened sense of well-being and improved mood using the Daily Menopausal Rating Scale during the treatment months than before treatment.⁴⁰ The group receiving the higher dose of CEE and placebo also reported significantly better psychological ratings when compared to the group on 0.625 mg CEE with MPA.⁴⁰

It must be emphasized that all these clinical trials used different HRT strategies, including various forms of estrogens, progestins, and androgens with varying routes of administration. Several researchers have noted that progestins have a negative effect on mood resulting in increased depression scores.^{37,40} This mechanism might not only be directly related to the sedative and anesthetic effects of progesterone on CNS neurotransmitters but also by estrogen receptor depletion and increasing MAO activity. Androgens have been shown to enhance mood possibly by their “energizing properties” and by aromatization to estrogen in the CNS.⁴¹ Cyclic mood and behavioral symptoms have been associated with sequential HRT and may improve with a switch to continuous combined estrogen plus progestin therapy.¹⁴ Several studies have concluded that the administration of transdermal estrogen, rather than an oral route, has a more positive effect on psychological symptomatology because 5-HT

is more effectively induced by the consistent and continuous low delivery of estrogen.⁴² Supra-physiological levels of estrogen actually down-regulate estrogen receptor activity.¹¹ The use of an endogenous estrogen, 17 β -hydroxyestradiol, either transdermal or oral, has shown it to be more effective than CEE for the improvement of depressed mood.⁶ Treatment with other estrogens rarely used as ERT, such as ethinyl estradiol and estriol, also showed an increase in blood 5-HT levels in postmenopausal women.³⁰

FURTHER EVIDENCE OF ANTIDEPRESSANT NATURE OF ESTROGEN

There are numerous clinical reports which further support the antidepressant nature of estrogen. Four women with no prior psychiatric illnesses developed panic disorder and/or major depression with and without psychotic features while receiving gonadotropin releasing hormone (GnRH) agonists for treatment of endometriosis.⁴³ Three of the four responded well with administration of sertraline, a SSRI.⁴⁵ Rapid mood cycling has been acknowledged as a complication of therapy with antidepressant medications and has been found with estrogen as well.⁴⁴ There is a case report of a postmenopausal woman with severe depression who developed rapid cycles of euthymia, hypomania, and depression when started on CEE with abrupt cessation of the mood cycling when her ERT was stopped.⁴⁴ A group of women with major depression, who had a history of a good response with antidepressants, failed treatment for their recurrent depression after they had been placed on tamoxifen, an antiestrogen.⁴⁵ There is only one case study of high dose CEE (15 to 25 mg doses) being used effectively as an antidepressant in a group of 23 severely depressed pre- and postmenopausal patients who were unresponsive to other more conventional modalities.³³

If decreasing levels of estrogen in the CNS account for the increased risk of depression in women, then this would help explain why men are at a reduced risk for affective disorders. Testosterone levels in men are nearly 1,000 times greater than plasma concentrations of E2 in women.²⁶ Aromatization of this androgen into 17 β -E2 in the CNS would result in brain levels of this estrogen just as high as those seen in women.²⁶ But aging men do not have the abrupt drop in plasma sex hormone levels that are seen in women

going through the menopause.²⁶

CONCLUSION

Researchers seem to agree that ERT enhances mood in peri- and postmenopausal women and can be considered to have a “mental tonic” effect. Estrogen is probably not as effective as a sole treatment for clinically recognized mood disorders.¹⁶ I believe that the use of ERT in mild depression is an appropriate initial step in the peri- and postmenopausal woman who needs treatment for concurrent vasomotor symptoms as well as for the cardiovascular, musculoskeletal, and genitourinary benefits. Progestin components must be added if there is a uterus, but adjustments in times of administration and dosage can minimize their negative effects. If after several months there is no change in mood, an antidepressant with or without psychological counseling should be added. It is possible that a lower dose of antidepressant will be required in a peri- or postmenopausal woman already on ERT.^{24,44} Investigations are currently in progress to further identify estrogens’ CNS effects with regard to the pathophysiology and appropriate treatment of affective disorders.

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Transdermal Hormone Replacement Therapy

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The value of hormone replacement therapy (HRT) for postmenopausal women is well established. Nonetheless, a minority of women in the United States, and far fewer worldwide, avail themselves of this treatment.¹ Even among those who elect to initiate hormone use, many discontinue due to side effects and/or anxiety about risks.²

One approach to improving acceptance and compliance is to increase awareness among health care providers and their patients of estrogen's role in health maintenance for women whose ovaries are no longer producing this hormone. Another tactic is the introduction of new vehicles for delivery. Although there are currently a variety of oral formulations, as well as a few vaginal/uterine preparations, additional options are likely to improve long-term utilization. While Transdermal Delivery Systems (TDS) containing estrogen have been on the market for several years, the recent availability in the United States of TDS which contain a progestin as well as estrogen greatly expands the population

for whom transdermal medication is suitable.

This survey will briefly review the accepted benefits of HRT, highlighting those for which transdermal treatment consistently improves or detracts from an anticipated response. Side-effects and detrimental health outcomes will be summarized, emphasizing areas where transdermal agents confer different expectations (Table 1).

A list of FDA-approved estrogen and estrogen/progestin transdermal agents available in the United States is provided (Table 2).

VASOMOTOR SYMPTOMS

All currently marketed HRT has clear efficacy in the reduction of hot flushes and night sweats associated with estrogen deprivation. Marked alleviation of these common concerns of women in their fourth and fifth decades of life has been reported with oral, vaginal, injectable, and transdermal formulations. Relief is rapid, with a complete response reported by most women within several weeks. As such symptoms abate, most women also report improved sleep. Addition of a progestin does not negate this benefit.³

INSOMNIA

A common complaint of women experiencing loss of ovarian function is insomnia. Measurable reduction in rapid eye movement sleep and increased sleep latency have been demonstrated. Use of oral or transdermal exogenous estrogen with⁴ or without a progestin results in improved rest patterns for most women. Although difficult to define, "quality of life" is generally reported to be improved when sleep quality is restored.

GENITO-URINARY ATROPHY

Estrogen depletion results in atrophic changes in the vagina, urethra, and bladder. Associated symptoms include dysuria, hematuria, urge and/or stress incontinence, dyspareunia, and atrophic vaginitis. As a further aggravation, loss of collagen leads to relaxation of the pelvic floor in susceptible women. Although aging per se contributes to the loss of pelvic support, estrogen replacement will significantly modify all of these genitourinary problems.⁴ Estrogen given in any form, including transdermally, readily provides symptomatic improvement for most women. Progesterone does not appear to modify this response.

strated health benefit of estrogen replacement is the maintenance of bone density. When bone strength is conserved, fracture risk should be greatly reduced. Estrogen is an anti-resorptive agent and reduces osteoclast activity. The Postmenopausal Estrogen/Progestin Interventions (PEPI) trial⁵ utilized serial dual-energy x-ray absorptiometry to demonstrate the protective effect of oral estrogen on bone density. In this investigation, estrogen alone or in combination with medroxyprogesterone acetate (MPA) continuously or cyclically, as well as estrogen in combination with cyclic oral micronized progesterone, all increased bone density.

Subsequently, research with transdermal estrogen patches and combination estrogen and norethindrone acetate patches has demonstrated similar maintenance of bone mineral density.⁶ Markers of bone formation (serum total osteocalcin and bone-specific alkaline phosphatase) and urine markers of bone resorption (C-telopeptide/creatinine ratio and N-telopeptide/creatinine ratio) all confirm the bone sparing effect of transdermal hormones.

METABOLIC EFFECTS OF ESTROGEN

As noted above, osteoporosis is associated with enormous morbidity among postmenopausal women. However, declining cardiovascular health is the leading cause of death in this population. Morbidity attributed to diseases of the cardiovascular system is also tremendously consequential. Current HRT use is associated with a significant risk reduction.⁷ The impact of estrogen on cardiovascular health through four different metabolic effects should be understood.

Lipoproteins: Adverse lipoprotein profiles associated with an increase in the occurrence of cardiovascular events are present in the hypoestrogenic, postmenopausal female. The utilization of oral estrogen replacement therapy (ERT) is associated with a 50% reduction of risk. The necessary addition of a progestin for those with an intact uterus minimally reduces this protection. The PEPI trial has documented the beneficial effects of oral estrogens with and without the addition of cyclic progestin or progesterone on low-density (LDL) and high-density (HDL) lipoproteins.⁸ Conversely, the effect on triglycerides was shown to be detrimental.

The use of transdermal HRT lowers

Table 1: Characteristics of Oral vs. Transdermal Hormone Preparations

| | Transdermal | Oral |
|-----------------------------------|-------------|------|
| Cholesterol | | |
| HDL | ↔ | ↑ |
| LDL | ↓ | ↓↓ |
| Triglycerides | ↓↓ | ↑ |
| Antithrombin III | ↔ | ↓ |
| Insulin resistance | ↔ | ↑ |
| IGF-1 | ↔ | ↓ |
| Growth hormone | ↔ | ↑ |
| Whole body fat mass | ↔ | ↑ |
| Lean body mass | ↔ | ↓ |
| Renin substrate | ↔ | ↑ |
| Mean blood pressure | ↓ | ↓ |
| MENQOL quality of life assessment | ↑ | ↑ |

OSTEOPOROSIS

Osteoporosis contributes to significant health care utilization in the United States today. The National Osteoporosis Foundation estimates that at least 5 million women have osteoporosis with millions more at risk. Approximately one and a half million fractures occur annually due to osteoporosis. Quality of life is impacted for women with fractures as a result not only of pain, but of lost wages, decreased mobility, and inability to function at home or participate in leisure activities. Particularly in the case of hip fractures, personal independence is compromised and other health problems ensue. As the population of this country ages, osteoporosis will become an even greater concern and cost.

A decline in bone mineral density parallels waning estrogen secretion in women. Perhaps the most clearly demon-

LDL (to a lesser extent than oral) while not increasing HDL cholesterol. Triglycerides are significantly reduced in women using a TDS containing both estradiol and norethindrone acetate.³ A transdermal preparation may be useful for patients with hypertriglyceridemia. Lipoprotein (a) also was found to be lower among women on a mid dose (estradiol 0.050 mg/norethindrone acetate 0.250 mg) patch.

Haemostasis: Oral contraceptive users and, to lesser extent, postmenopausal users of oral estrogen⁹ have an increased risk of venous thrombotic events. Estrogens have both pro- and anti-coagulant effects. Oral estrogens beneficially increase plasminogen and fibrinolytic activity. They simultaneously decrease levels of the potent natural anticoagulant, antithrombin III, while increasing mean values of prothrombin activation peptide F1+2, a marker of thrombin generation.¹⁰

No long-term data on the likelihood of thrombosis with transdermal estrogens exists. However, in a prospective comparison, conjugated equine estrogen resulted in the anticipated decrease in antithrombin III, while an estradiol patch did not have a significant effect.¹¹ In time, epidemiologic studies will determine the clinical relevance of this theoretically beneficial difference.

Glucose/insulin: The risk of cardiovascular disease is increased in persons with glucose intolerance and insulin resistance. Although there are conflicting reports concerning carbohydrate metabolism and the use of oral estrogen, an increased secretion of growth hormone (GH), which impairs insulin action, has been demonstrated.¹² Growth hormone secretion did not significantly change with a transdermal preparation. Neither treatment modality affected glucose or insulin levels during a glucose tolerance test, but an improvement of insulin action on lipid metabolism was identified with the estradiol TDS.

The route of estrogen administration may impact fat and lean body mass.¹³ In addition to an increase in GH, ingestion of oral, but not transdermal, estrogen suppresses lipid oxidation and decreases insulin-like growth factor-1 (IGF-1). Reduction of the potent anabolic actions of circulating IGF-1 may explain the decrease in lean body mass with a concomitant increase in whole body fat mass demonstrated only with oral ERT. An

increase in body volume will be associated with a shift in body composition from denser lean to lighter fat tissue. This change in volume could be associated with the self perception of adiposity often reported by oral estrogen users.

Renin/angiotensin: Hypertensive women are four times more likely to develop cardiovascular disease. Even though oral estrogens increase circulating renin substrate, a consistent adverse effect on blood pressure has not been confirmed. Since non-oral preparations avoid the hepatic first-pass effect, their use should not be associated with any stimulation of renin substrate. Therefore no increase in blood pressure is anticipated. An estradiol TDS has been shown to lower mean ambulatory blood pressure in both normotensive¹⁴ and hypertensive¹⁵ postmenopausal women.

DEMENTIA, MEMORY, COGNITIVE FUNCTIONING

Estrogen replacement is associated with

an improvement in cognition and short-term memory as well as a decrease in the incidence of dementia. A prospective trial of attention, orientation, mood, and social interaction among women with senile dementia-Alzheimer's type showed significant improvement.¹⁶ An experimental animal model has demonstrated the ability of estrogen to prevent neuronal loss.¹⁷ Progesterone neither suppressed nor potentiated this action. Theoretically transdermal hormones should be likewise effective in the deterrence of dementia, but there is no published data on this topic. With the demonstration of an association between increased serum insulin and decreased cognitive function and dementia in women,¹⁸ transdermal preparations may actually be preferential via their protection of GH and insulin levels.¹³

QUALITY OF LIFE

Quality of life issues are complex, difficult to define, and particularly challenging

Table 2: Transdermal Hormonal Preparations

| Preparation | Manufacturer | Dosage |
|---------------------------------|-----------------------------|--------------------------------------|
| Estrogen only | | Estradiol |
| Alora* | Procter & Gamble | 0.05, 0.075, 0.1 mg/d |
| Climara† | Berlex | 0.05, 0.1 mg/d |
| Estraderm* | Novartis | 0.05, 0.1 mg/d |
| Fem-Patch* | Parke-Davis | 0.025 mg/d |
| Vivelle* | Novartis | 0.0375, 0.05, 0.075, 0.1 mg/d |
| Estrogen & progestin | | |
| CombiPatch 50/140* | Rhône-Poulenc | 0.05 mg estradiol / 0.140 mg |
| | Rorer | norethindrone acetate |
| CombiPatch 50/250* | | 0.05 mg estradiol / 0.250 mg |
| | | norethindrone acetate |
| *apply twice weekly | | |
| †apply weekly | | |

to measure objectively. Nonetheless, estrogen replacement is commonly believed to improve quality of life for the postmenopausal woman.

In general, good physical health can be agreed upon as contributing to optimum quality of life. Another quality of life issue, sexual functioning, is adversely affected among some postmenopausal women.²⁴ Complaints include vaginal dryness, dyspareunia, decrease in clitoral sensitivity, decrease in orgasm intensity, and decrease in orgasmic frequency. Estrogen is known to increase the thickness of the vaginal epithelium and improve vaginal lubrication. Specific improvement in sexual function with oral estrogen has been documented.¹⁹ While on treatment, 90% of women reported an increase in level of desire and an increase in sexual activity. Although such a study has not been performed among users of transdermal hormones, it is anticipated that any form of absorbed estrogen would have beneficial effects.

Sexual function is only one of several quality of life issues assessed by an instrument known as the MENQOL (menopausal quality of life measure). The 29 menopause-specific items also evaluate vasomotor, psycho-social, and physical well being. When this tool was utilized in a study of women placed on either oral or transdermal estrogen (both groups also received cyclic MPA), improvement was seen in all domains. There was a significant main effect of duration of therapy, with no differences between the two forms of estrogen.²⁰

SIDE-EFFECTS

Adversely affecting quality of life are the potential negative effects of hormone replacement. These are few, but anxiety associated with these effects is substantial. Nuisance side-effects are frequent when treatment is being initiated. For most women such problems as breast soreness and irregular bleeding can be eliminated through adjustment of dose and/or estrogen/progestin ratio. Notable differences have not been established between oral and transdermal preparations in this regard. A small number of women complain of nausea with ERT. Usually, a change in time of ingestion eliminates this problem. Transdermal treatment may be helpful for some users.

Fortunately, most women with migraine headaches find relief on hor-

mone replacement. If exacerbation of headaches does occur, changing the time of ingestion of an oral preparation or taking advantage of the more steady delivery of estrogen via a skin patch is often successful. It is important not to subject women with headaches to drug-free intervals. Continuous application of the estrogen or estrogen/progestin is preferable.

Skin reactions occur in some women using transdermal hormonal preparations. As matrix patches have replaced alcohol containing reservoir systems, this complaint has become uncommon.³ Rarely, even with good application and site rotation, unacceptable erythema and pruritus necessitate discontinuation. True allergic reactions may occur with any delivery system. These are usually a reaction to the vehicle and not the hormone and should be approached with this in mind.

RISKS

Of great concern to women and physicians contemplating the use or prescription of HRT is the possible association of breast cancer with current HRT use. Although there are publications describing no relationship, others appear to demonstrate a risk in the range of one additional case for each 500 to 600 users.²¹ Certain populations of women are at greater risk due to modifiable (e.g., alcohol intake or obesity) or unmodifiable (e.g., family history) factors. It is heartening to note that long-term survival among women who have breast cancer diagnosed while on an HRT regimen is excellent. Due to the relatively short time that transdermal hormone preparations have been in use, the exact rate of breast cancer among patients on this treatment has not been established. There is no theoretical reason however to expect any difference in risk compared to oral therapy.

Oral estrogen users are reported to have a two times increase in their risk of gall bladder disease.²² Although an increase in hepatic activity is experienced by oral vs. transdermal estrogen users, risk factors for cholelithiasis have been shown to be similar between the two populations.²³ This finding suggests there would be no difference in risk. There are, however, no epidemiologic data to confirm or refute this expectation.

With widespread use of HRT, disparity between benefit and risk for most serious complications and/or nuisance side-effects will probably prove to be more dependent

on characteristics of the treated individual than on specific formulations or routes of delivery. However, as a generalization, increasing dosage is associated with both an increase in risks and in side-effects; while maximal dosages usually do not increase the anticipated value.⁷

CONCLUSION

Women for whom transdermal hormone therapy should be specifically considered include those with hypertriglyceridemia, hypertension, persistent headaches, poor absorption of any oral medication, and/or perceived weight gain on oral preparations. Women at risk for venous thrombosis and those with insulin resistance may also benefit from this treatment. For the majority of postmenopausal women, estrogen use offers major health benefits, improves quality of life, and bears few risks. Unfortunately, fewer than one-third of women who are eligible for such treatment presently take advantage of it. The recent increase in dosing options and delivery vehicles should contribute to a parallel increase in acceptability and utilization. This should markedly improve life for many older women.

The author has revealed the following potential conflict of interest: Rhone-Poulenc Rohrer Consultant and Speakers Bureau.

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Menopausal MEDICINE

Volume 7, Number 3, Fall 1999

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