

# American Society for Reproductive Medicine Menopausal MEDICINE

Volume 7, Number 1, Spring 1999

FOR CLINICIANS WHO PROVIDE CARE FOR WOMEN

## Estrogen and Alzheimer's Disease: Current Status

**Victor W. Henderson, M.D., M.S.**

Professor of Neurology, Gerontology, and Psychology, University of Southern California, Los Angeles, CA; Grant Recipient: National Institutes of Health, Alzheimer's Association, Wyeth-Ayerst Laboratories, French Foundation for Alzheimer Research; Consultant: Organon, Procter and Gamble, Lilly Research Laboratories

### INTRODUCTION

Normal or "usual" aging is often accompanied by a decline in certain cognitive skills. These age-associated decrements are relatively modest. In contrast, dementia represents the substantial loss of mental abilities severe enough to interfere with daily affairs. Dementia is increasingly prevalent with advancing age, with the number of affected persons doubling about every five years in the seventh through ninth decades of life. Among the numerous causes of dementia, Alzheimer's disease (AD) is by far the most common, accounting for approximately two-thirds of all cases. The prevalence of AD is about 1.5 to 3 times greater among women than men, in part simply because there are more older women in the elderly age group at greatest risk for AD, in part because women with symptoms of AD survive somewhat longer than men with this disorder, and in part because women may be more vulnerable to developing Alzheimer symptoms in the first place. For older women, the possibility of AD is a frightfully real concern.

AD is increasingly viewed as a syndrome with multiple determinants.<sup>1</sup> However, except for age at symptom onset, clinical and pathological features of AD are similar regardless of pathogenesis.

### IN THIS ISSUE

Estrogen and Alzheimer's Disease: Current Status	1
Effects of Estrogens and Androgens on the Libido of Women Following Surgical and Natural Menopause	5
Consumer Ambivalence and the Role of the Physician in Counseling	9

When symptoms first emerge before age 60 years, as occurs in about 5% of all AD cases, the underlying cause is often a point mutation in one of the genes encoding for the presenilin proteins (chromosomes 14 and 1) or in the gene encoding for the amyloid precursor protein (chromosome 21). These mutations are highly penetrant and are transmitted in an autosomal dominant manner. Late-onset AD, representing the vast majority of all Alzheimer cases, is not dominantly inherited. Rather, it is likely that a number of so-called susceptibility genes modify the risk of dementia. The best known susceptibility gene is on chromosome 19 and encodes for a glycoprotein known as apolipoprotein E. One function of apolipoprotein E is to shuttle lipids during neuronal repair. Apolipoprotein E exists in three common variants, or polymorphisms, with increased risk conferred by the  $\epsilon 4$  allele. Approximately 15% to 20% of persons of European extraction possess at least one copy of this common allele.

A number of nongenetic factors are also conjectured to heighten Alzheimer risk. In addition to advanced age, these risk factors include female gender, low educational attainment, prior head injury, absence of exposure to anti-inflammatory medications, and (for women) absence of exposure to exogenous estrogen after the menopause. Recent evidence pertaining to

## FROM THE EDITOR

*David F. Archer, M.D.*

Women seek hormone replacement therapy for real problems such as hot flashes, sleep disturbances, and irritability. Physicians know that HRT will treat these conditions. Dr. Graziottin indicates that counseling of the menopausal woman regarding hormone replacement therapy is an art. Physicians need to be willing to devote the time and effort to this aspect of counseling. Putting information into a context useful for the consumer can be difficult. The consumer does require a clear delineation of benefits and risks of HRT as part of a preventative health strategy.

Dr. Henderson presents the current status of estrogen and Alzheimer's disease. This is a provocative article on hormonal effects on central nervous system function and its potential relationship to a reduction in Alzheimer's disease. As he states, these data, if confirmed, would have significant Public Health consequences.

Dr. Weber has evaluated the role of estrogens and androgens on libido in postmenopausal women. Recent interest has focused on libido in older women, perhaps as part of the introduction of a treatment for the impotent male (Viagra). She indicates that female libido is a complex issue involving both hormones and psychosexual orientation. This topic deserves increased awareness by the physicians caring for older women.

# Menopausal Medicine

A Newsletter of the  
American Society for Reproductive Medicine



## OFFICERS

President	Larry I. Lipshultz, M.D.
President-Elect	R. Jeffrey Chang, M.D.
Past President	Arthur F. Haney, M.D.
Secretary	Thomas T.F. Huang, Jr., Ph.D.
Treasurer	Stuart S. Howards, M.D.
Executive Director	J. Benjamin Younger, M.D.
Medical Director	Roger D. Kempers, M.D.
Administrative Director	Nancy C. Hayley

## DIRECTORS

Ricardo Azziz, M.D., M.P.H.  
Marian D. Damewood, M.D.  
Mary Lake Polan, M.D.  
Robert S. Schenken, M.D.  
Ana A. Murphy, M.D.  
Robert J. Stillman, M.D.

## EDITOR

David F. Archer, M.D.  
Professor of Obstetrics and Gynecology,  
Director, Clinical Research Unit, Eastern  
Virginia Medical School, Norfolk, Virginia

## EDITORIAL BOARD

Kamran S. Moghissi, M.D.  
Professor and Emeritus Director, Department  
of Obstetrics and Gynecology, Division of  
Reproductive Endocrinology, Wayne State  
University School of Medicine and Hutzel  
Hospital, Detroit, Michigan

Leon Speroff, M.D.  
Professor of Obstetrics and Gynecology, Oregon  
Health Sciences University, Portland, Oregon

Robert A. Wild, M.D., M.P.H.  
Professor and Chief, Section of Reproductive  
Endocrinology, Department of Obstetrics and  
Gynecology, Adjunct Professor of Medicine  
(Cardiology), Epidemiology, Chief, Gynecology  
Section, Veterans Affairs Medical Center, University  
of Oklahoma Health Sciences Center, Oklahoma  
City, Oklahoma

## MANAGING EDITORS

Jennifer Kelly  
Michele M. Parker

The ASRM is pleased to acknowledge the generous  
contribution of Wyeth-Ayerst Laboratories toward  
the publication of this  
newsletter.



Copyright 1999  
American Society for Reproductive Medicine

estrogen and AD is summarized below, with particular emphasis given to data germane to Alzheimer risk.

## THE BRAIN AS A TARGET ORGAN FOR ESTROGEN

Subpopulations of neurons within the brain express intranuclear receptors for estrogen, and estrogen has clear effects on brain function<sup>2</sup> (Table 1). There are two receptor types, alpha and beta, and a given neuron can express the alpha estrogen receptor, the beta receptor, both receptor types, or neither. As with other steroid hormones, estrogen binding to its receptor leads to the transcriptional regulation of specific gene products. Estrogen also influences cerebral functions indirectly. Some of these actions, such as effects on neuronal excitability or neurotransmitter release, do not involve classic intranuclear receptors but may involve receptors on the cell membrane. In select neuronal populations, estrogen can act to enhance cell differentiation, neurite growth, and synaptic plasticity. Estrogen also promotes neuronal survival. Estrogen may protect against programmed cell death (apoptosis), a postulated mechanism of neuronal loss in Alzheimer brain. Antioxidant and anti-inflammatory properties are neuroprotective, and estrogen augments both cerebral blood flow and the active transport of glucose into the brain. Cortisol may deleteriously affect hippocampal neurons, and estrogen blunts corticosteroid elevations induced by stress.

Estrogen influences several neurotransmitter systems, including acetylcholine, whose activity may be modulated by estrogen. Within the basal forebrain region, cholinergic neurons vulnerable to AD pathology express receptors for estrogen. In experimental animals, ovariectomy reduces cholinergic activity in the brain, whereas estrogen therapy restores markers of cholinergic function. In both human and laboratory animals, cholinergic deficits are linked to memory impairment, and estrogen reverses learning deficits experimentally induced by a cholinergic antagonist.

The  $\beta$ -amyloid protein, whose deposition is a biochemical hallmark of AD neuropathology, is derived from abnormal metabolism of the amyloid precursor protein. Estrogen reduces formation of the  $\beta$ -amyloid fragment. Within select brain regions, estrogen also increases the expression of apolipoprotein E by resident glial cells.

## ESTROGEN EFFECTS ON COGNITION AND MOOD

Estrogen influences certain mental processes.<sup>2</sup> Cognitive abilities may fluctuate somewhat during a woman's menstrual cycle, with some reports suggesting relatively greater articulatory agility, verbal fluency, or creativity during follicular or luteal phases than during the menses. Interestingly, verbal fluency may be enhanced in trans-sexual males given an anti-androgen plus estrogen.

After the menopause, the ovaries no longer produce estrogen, and circulating levels of estradiol and estrone decline sharply. In several cohorts of older women, current estrogen use was linked to better cognitive scores.<sup>3,4</sup> Other investigators, however, have failed to substantiate a meaningful impact of estrogen therapy on cognition,<sup>5</sup> and among postmenopausal women there is no evidence that relatively higher serum levels of estradiol or estrone protect against cognitive decline associated with age.<sup>6</sup>

Results of randomized controlled trials of estrogen replacement therapy provide stronger evidence that estrogen enhances certain cognitive abilities. It is important to bear in mind, however, that the magnitude of improvement seen in most studies is modest. The most consistent positive finding has involved verbal memory (for example, the ability to recall information from a paragraph-length story). One investigation, for example, assessed women whose ovarian function had been suppressed with a gonadotropin releasing hormone agonist (leuprolide).<sup>7</sup> In this study, after subjects were given leuprolide, circulating levels of estrogen fell and verbal memory declined.

**TABLE 1.** Estrogen Actions that Influence Brain Function or May Impact Alzheimer's Disease\*

**Neurotrophic effects:** Neuronal differentiation, Extension of nerve processes, Synapse formation

**Neuroprotective effects:** Protection against apoptosis, Modulation of neurotrophic factors, Antioxidant properties, Anti-inflammatory effects, Increased cerebral blood flow, Enhanced transport of glucose across the blood-brain barrier, Blunted cortisol response to psychological stress

**Effects on neurotransmitters:** Acetylcholine, Noradrenaline, Serotonin, Dopamine, Glutamate, Gamma aminobutyric acid

**Effects on proteins implicated in Alzheimer's disease:** Decreased formation of  $\beta$ -amyloid, Increased expression of apolipoprotein E within the brain

Memory scores subsequently returned to baseline in women given estrogen in addition to leuprolide, but scores remained depressed in those for whom leuprolide was supplemented only with placebo.

In addition to effects on cognition, estrogen also impacts mood. Small randomized clinical trials indicate that estrogen can improve mood in postmenopausal women with clinical depression<sup>8</sup> and in healthy women without a disturbance in mood.<sup>9</sup> Mechanisms by which estrogen might impact mood are unknown, but estrogen affects both serotonin and noradrenaline, two neurotransmitter systems that are targeted by anti-depressant medications.

### ESTROGEN EFFECTS ON COGNITION IN ALZHEIMER'S DISEASE

There is preliminary evidence that estrogen might favorably impact symptoms of AD. In one observational study, women with AD receiving estrogens performed substantially better on a variety of neuropsychological measures than a matched group of demented women not receiving estrogen.<sup>10</sup> Cognitive performance differences in this study were unrelated to mood. In a brief (three week) double-blind study of oral conjugated estrogens, women in the active treatment group improved significantly over baseline on three psychometric measures, whereas demented women in the placebo group were unchanged.<sup>11</sup> Cognitive improvement was also suggested in a five-month open label

study of conjugated estrogens.<sup>12</sup> Interactions with the cholinergic system may be important in this respect; post hoc analysis from a multicenter study of a cholinomimetic drug in AD suggests that concomitant estrogen therapy might have augmented cognitive effects of the cholinergic medication.<sup>13</sup> As recently reviewed,<sup>14</sup> results of clinical trials of estrogen in AD are encouraging, but studies to date have been limited by small sample sizes and often by the absence of a placebo group. Results from larger randomized placebo-controlled trials of estrogen, some of which are anticipated in the near future, may provide more clear-cut answers with regard to AD therapy.

### ESTROGEN THERAPY AND THE RISK OF ALZHEIMER'S DISEASE

Over the past few years, exploratory analyses have raised the possibility that estrogen deficiency predisposes to AD. Although there is no consistent relation between age at menopause and AD, women with AD are less likely to use estrogen than older women without dementia, and more importantly, the use of estrogen replacement after the menopause is associated with a reduced risk of developing Alzheimer symptoms<sup>14,15</sup> (Table 2).

Recent case-control and cohort studies summarized in Table 2 imply that estrogen replacement provides partial protection against AD.<sup>14,16</sup> Some limitations of these studies should be acknowledged, however.

Exposure misclassification could have occurred if information on estrogen usage was collected retrospectively, after some women had already developed symptoms of dementia. In a few instances, the temporal sequence between estrogen exposure and AD onset was uncertain, and estimates were based on current estrogen use. In this circumstance, risk estimates could have been biased if a woman's physician viewed estrogen as a discretionary medication that should be discontinued in the presence of dementia or, conversely, if a physician prescribed estrogen in the hope of palliating dementia symptoms. In some reports, bias could have occurred when information on estrogen exposure was obtained differently for AD cases (when the informant was a family member or other proxy) than for control subjects (when the woman herself was the informant).

The most recent epidemiological study of estrogen and AD is from the Italian Longitudinal Study on Aging.<sup>17</sup> In this population-based sample of over 2,000 older women, 92 cases of AD were identified. The use of estrogen after the menopause was linked to reductions in AD risk of more than 70%.

The largest epidemiological study in which information on estrogen exposure was collected prospectively is a nested case-control study from the Leisure World retirement community in southern California.<sup>18</sup> At the time of their enrollment in the early 1980s, almost 9,000 women in this middle-class cohort self-reported detailed information on past and current hormone use. Based on subsequent death certificate records obtained through 1995, 248 cohort members were identified as having AD, and their estrogen use was compared to that of 1,198 women without a dementia diagnosis on their death records. Results of this analysis showed that women in Leisure World who had taken estrogen had a risk of AD one-third lower than that of women who had never used estrogen replacement. Different routes of estrogen administration were each associated with significantly lower Alzheimer risks.

In addition to Leisure World, four other AD studies have used prospectively collected information on estrogen exposure. These were from the Puget Sound region of Washington state, New York City, Baltimore, and Rochester, Minnesota. The Puget Sound case-control study did not discern a significant association between estrogen and AD, but findings from New York, Baltimore, and Rochester each suggested risk reduc-

**TABLE 2.** Estrogen Replacement Therapy and the Estimated Risk of Developing Alzheimer's Disease: Recent Case-Control and Cohort Studies\*

Author, year†	Study location	Risk estimate	95% confidence interval
Birge, 1994	St. Louis, MO	0.07	not stated
Henderson et al, 1994	Los Angeles, CA	0.33	0.15 - 0.74
‡Paganini-Hill&Henderson, 1994	Leisure World, CA	0.69	0.46 - 1.03
†Brenner et al, 1994	Puget Sound, WA	1.1	0.6 - 1.8
Mortel & Meyer, 1995	Houston, TX	0.55	0.26 - 1.16
Lerner et al, 1996	Cleveland, OH	0.41	0.12 - 0.69
‡§Paganini-Hill & Henderson, 1996	Leisure World, CA	0.65	0.49 - 0.88
‡Tang et al, 1996	New York City, NY	0.5	0.25 - 0.9
van Duijn et al, 1996	Rotterdam, The Netherlands	0.40	0.19 - 0.91
‡Kawas et al, 1997	Baltimore, MD	0.46	0.209 - 0.997
‡Waring et al, 1997	Rochester, MN	0.4	0.2 - 0.8
Baldereschi et al, 1998	Italy	0.28	0.08 - 0.98

\* Estrogen therapy includes both unopposed estrogen and estrogen opposed by a progestogen. Four case-control studies before 1991 showed no significant association between estrogen and Alzheimer's disease. A risk estimate of less than one implies that estrogen replacement protected against Alzheimer's disease. When the entire 95% confidence interval is also less than one, the association between estrogen use and Alzheimer's risk reduction is statistically significant ( $P < 0.05$ ).

† Study references, except for Kawas et al,<sup>19</sup> Waring et al,<sup>20</sup> and Baldereschi et al,<sup>17</sup> are given in a recent review.<sup>16</sup>

‡ Studies in which information on estrogen use had been gathered prospectively.

§ Includes cases from the 1994 Leisure World analysis of Paganini-Hill and Henderson.

tions between 50% and 60% among women who had used estrogen (Table 2). In each of these studies, AD ascertainment was based on a physician's clinical assessment.

The demonstration of an association between estrogen use and AD risk reduction in most of the recent reports (Table 2) does not in itself prove that estrogen replacement prevents AD, or more-or-less equivalently, that estrogen replacement delays the onset of AD symptoms. However, a causal inference is strengthened if it turns out that greater estrogen exposure is associated with greater protection against AD. Several epidemiological studies have in fact collected quantitative information on estrogen use. In the negative Puget Sound study, as well as in the otherwise positive Baltimore study, there was no significant association between the magnitude of estrogen exposure and the degree of Alzheimer risk reduction. However, significant associations were reported in three other positive studies. In Leisure World, risk estimates for AD decreased significantly with increasing dose of the longest used oral estrogen preparation, as well as with increasing duration of estrogen use<sup>18</sup> (Figure 1). For the higher dose range ( $\geq 1.25$  mg per day of conjugated estrogens), the risk estimate was 0.54 (95% confidence interval [CI] = 0.32 to 0.92); for women who used estrogen replacement for at least 15 years, the estimate was 0.44 (95% CI = 0.26 to 0.75). In the community-based New York City cohort, women who had used oral estrogen for longer than one year had greater risk reductions than women who had used estrogen for less than a year. In Rochester, risk estimates decreased with increasing duration of estrogen use and

with increasing total cumulative dose of estrogen.

### ESTROGEN, APOLIPOPROTEIN E, AND ALZHEIMER'S RISK

As already noted, polymorphisms of apolipoprotein E have an important influence on the risk of AD, although mechanisms for this association are not yet well understood. Interestingly, increased risk conveyed by the  $\epsilon 4$  allele may be greater for women than men. Because estrogen affects apolipoprotein E expression, it is conceivable that putative estrogen benefits may vary by genotype. This possibility has been considered in two studies, with conflicting findings. In the New York City cohort, estrogen use after the menopause was observed to be protective regardless of genotype. Among women who were heterozygous for the  $\epsilon 4$  allele, the risk estimate was 0.13 (95% CI = 0.02 to 0.95), and for women without this allele the Alzheimer risk was 0.4 (95% CI = 0.2 to 0.9). Unlike in New York, the Rotterdam case-control study included only women with early-onset symptoms of dementia. As in New York, estrogen use was associated with a significantly reduced risk of AD, but the protective effect was evident only in women who possessed the  $\epsilon 4$  allele (the relative risk in this subgroup was 0.14 (95% CI = 0.02 to 0.87)). Although women in the New York study were older (the mean age of AD subjects was 78.5 years), it is not known why results were discrepant.

### CONCLUSION

Important issues remain unaddressed. In the years to come, the selective estrogen receptor modulators (SERMs), drugs that

bind to estrogen receptors but have agonist or antagonist effects in different target tissues, are apt to see increasing use in defined clinical populations. At present there are virtually no published data on how different SERMs might affect cerebral processes relevant to AD. For women with a uterus, estrogen is usually combined with a progestational agent. Within the brain, estrogen effects can be modulated by progesterone in either a positive or negative fashion, depending on the biological process under study. Effects of progestogens on AD are unknown, and future studies will need to address clinical actions of this important neurosteroid.

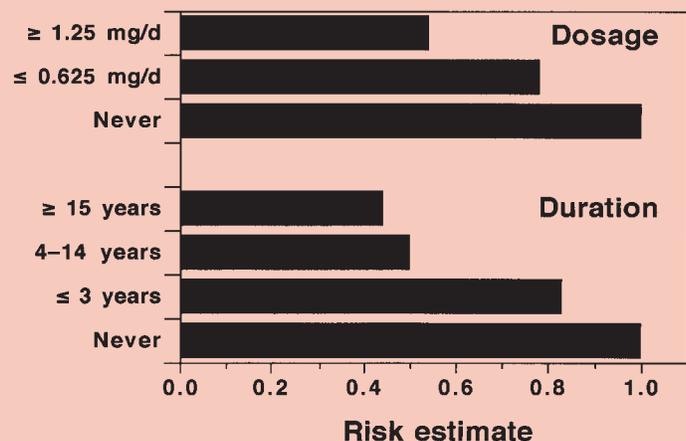
As reviewed above, there is a strong biological rationale for supposing that estrogen favorably impacts cerebral functions and physiological processes relevant to AD (Table 1). Moreover, there is accumulating epidemiological evidence to support the hypothesis that estrogen replacement reduces a woman's risk of developing AD. In most analytical studies since 1994, a woman's use of estrogen after the menopause is associated with a risk reduction of about one-half (Table 2). A risk reduction of this magnitude, which is equivalent to postponing the onset of AD by about five years, would have enormous public health implications. Moreover, within the range of estrogen exposures examined, women who used higher estrogen dosages or who used estrogen for longer periods of time appeared to enjoy even greater protection from AD (e.g., Figure 1).

Epidemiological data, albeit encouraging, are not irrefutable. It remains possible that unrecognized biases or confounding could suggest a positive association in the absence of any true protective effect. More secure knowledge will come from well-designed randomized controlled trials of AD prevention. One such ongoing trial is an ancillary study attached to the Women's Health Initiative under the auspices of the National Institutes of Health. The Women's Health Initiative Memory Study (WHIMS) involves almost 8,000 women who have been randomly assigned to receive oral conjugated estrogens (with or without continuous combined medroxy-progesterone acetate, depending on the presence or absence of a uterus) or placebo. Results of WHIMS are eagerly anticipated in about 2004.

### REFERENCES

1. Landon CL, Ashall F, Goate AM. Exploring the eti-

**FIGURE 1.** Effects of estrogen dosage and the duration estrogen treatment on the risk of Alzheimer's disease. In the Leisure World retirement community cohort, there was a significant relation between the relative risk for Alzheimer's disease and the longest used dose of oral conjugated estrogens ( $P < 0.01$ ) and the duration of estrogen therapy after the menopause ( $P < 0.001$ ). Data are from Paganini-Hill and Henderson, 1996.<sup>18</sup>



ology of Alzheimer's disease using molecular genetics. *JAMA*. 1997; 277:825-831.

2. Henderson VW. Estrogen, cognition, and a woman's risk of Alzheimer's disease. *Am J Med*. 1997;103(suppl 3A):11-18.

3. Schmidt R, Fazekas F, Reinhart B, et al. Estrogen replacement therapy in older women: a neuropsychological and brain MRI study. *J Am Geriatr Soc*. 1996;44:1307-1313.

4. Resnick SM, Metter EJ, Zonderman AB. Estrogen replacement therapy and longitudinal decline in visual memory. A possible protective effect? *Neurology*. 1997;49:1491-1497.

5. Barrett-Connor E, Kritiz-Silverstein D. Estrogen replacement therapy and cognitive function in older women. *JAMA*. 1993;269:2637-2641.

6. Yaffe K, Grady D, Pressman A, Cummings S. Serum estrogen levels, cognitive performance, and risk of cognitive decline in older community women. *J Am Geriatr Soc*. 1998;46:816-821.

7. Sherwin BB, Tulandi T. "Add-back" estrogen reverses cognitive deficits induced by a gonadotropin-releasing hormone agonist in women with leiomyomata uteri. *J Clin Endocrinol Metab*. 1996;81:2545-2549.

8. Klaiber EL, Broverman DM, Vogel W, Kobayashi Y. Estrogen therapy for severe persistent depressions in women. *Arch Gen Psychiatry*. 1979;36:550-554.

9. Ditkoff EC, Cray WG, Cristo M, Lobo RA. Estrogen improves psychological function in asymptomatic postmenopausal women. *Obstet Gynecol*. 1991;78:991-995.

10. Henderson VW, Watt L, Buckwalter JG. Cognitive skills associated with estrogen replacement in women with Alzheimer's disease. *Psychoneuroendocrin*. 1996;21:421-430.

11. Honjo H, Ogino Y, Tanaka K, et al. An effect of conjugated estrogen to cognitive impairment in women with senile dementia - Alzheimer's type: a placebo-controlled double blind study. *J Jpn Menopause Soc*. 1993;1:167-171.

12. Ohkura T, Isse K, Akazawa K, Hamamoto M, Yaoi Y, Hagino N. Low-dose estrogen replacement therapy for Alzheimer's disease in women. *Menopause*. 1994;1:125-130.

13. Schneider LS, Farlow MR, Henderson VW, Pogoda JM. Effects of estrogen replacement therapy on response to tacrine in patients with Alzheimer's disease. *Neurology*. 1996;46:1580-1584.

14. Henderson VW. Estrogen replacement therapy for the prevention and treatment of Alzheimer's disease. *CNS Drugs*. 1997;8:343-351.

15. Yaffe K, Sawaya G, Lieberburg I, Grady D. Estrogen therapy in postmenopausal women. *JAMA*. 1998;279:688-695.

16. Henderson VW. The epidemiology of estrogen replacement therapy and Alzheimer's disease. *Neurology*. 1997;48 (suppl 7):27-35.

17. Baldereschi M, et al. Estrogen-replacement therapy and Alzheimer's disease in the Italian Longitudinal Study on Aging. *Neurology*. 1998;50:996-1002.

18. Paganini-Hill A, Henderson VW. Estrogen replacement therapy and risk of Alzheimer's disease. *Arch Intern Med*. 1996;156:2213-2217.

19. Kawas C, Resnick S, Morrison A, et al. A prospective study of estrogen replacement therapy and the risk of developing Alzheimer's disease: the Baltimore Longitudinal Study of Aging. *Neurology*. 1997;48:1517-1521.

20. Waring SC, Rocca WA, Petersen RC, Kokmen E. Postmenopausal estrogen replacement therapy and Alzheimer's disease: a population-based study in Rochester, Minnesota. *Neurology*. 1997;48 (suppl 2):A79. Abstract.

# Effects of Estrogens and Androgens on the Libido of Women Following Surgical and Natural Menopause

**Asma A. Weber, M.D.**

Junior Associate Faculty, Department of Family Medicine, Eastern Virginia Medical School, Norfolk, VA

## INTRODUCTION

Aging and sexuality are not at opposite ends of a spectrum.<sup>1</sup> Although the frequency of sexual activity tends to decrease with age, an average of approximately 70% of healthy 70-year-olds continue to have sexual intercourse on a regular basis.<sup>2</sup> Therefore, the capacity and opportunity to engage in sexual behavior for non-reproductive purposes can be considered a quality of life issue.<sup>3</sup>

The desire for intimacy and sex continues into old age. Although the mechanism of sexual desire is still not fully understood, it has been suggested that testosterone (T) may modulate neurotransmitters in the central nervous system directly, which then play a role in promoting libido.

When women enter menopause, there is a gradual decline of estrogen and a slight increase in T secondary to ovarian stromal hyperplasia. This increase in T is time limited, and as the levels decrease by the fourth or fifth menopausal year, it contributes to complaints of decreased libido. Women who have undergone surgical menopause experience an abrupt loss of these hormones resulting in severe loss of libido. Estrogen may alleviate symptoms of hot flashes and vaginal dryness which may improve sexual function, but it has not been shown to have direct effects on arousal, desire, or libido; whereas restoring T has been demonstrated to significantly improve sexual drive and arousal.<sup>4</sup> Dehydroepiandrosterone (DHEA) has been shown to improve the overall feelings of well-being in elderly when given parenterally, which impacts greatly on the sense of sexual satisfaction. Apparently, DHEA is of little effect when given orally. More investigation is needed in this area.

There are also many other factors that can alter libido such as chronic illness, certain diseases, medications, depression, and social barriers. These factors need to be

considered when evaluating a patient complaining of decreased libido. Most importantly, physicians must become more accustomed to discussing sexual issues with patients as it can make a tremendous impact on their quality of life.

## SEXUAL DESIRE

The human sexual response cycle consists of three phases. Desire or libido is the motivational component. Excitement provides vaginal lubrication and congestion. That results in orgasm giving the pleasurable clonic contractions of genital muscles producing climax.<sup>4</sup> Sexual desire is an urge that impels women to seek out, initiate, and partake of sexual stimulation.<sup>5</sup> But sexual desire is not just a subjective sensation or merely a cognitive event. It is modified by social behavior, as well as central neurotransmitters in the brain.<sup>6</sup>

The mechanisms involved in T regulation of libido are not well understood. Studies by McEwen have shown neurons containing specific cytosolic receptors for estradiol 17-beta (E2) and T in particular areas of the brain. Estrogen receptors are predominantly located in the pituitary, hypothalamus, and limbic forebrain, whereas T receptors are found primarily in the preoptic area of the hypothalamus, with smaller concentrations in the limbic system.<sup>7</sup> Moreover, studies of non-human primates suggest T exerts effects on sexual desire via mechanisms that impact directly on the brain rather than by any effect on peripheral tissues.<sup>8</sup> T or a metabolite may modulate neurotransmitters in the central nervous system, which then play a role in promoting libido.<sup>9</sup>

## HORMONAL CHANGES IN MENOPAUSE

In women, both the adrenal and ovary contain the biosynthetic pathways necessary for androgen synthesis and secretion. The ovary produces 25% plasma T, 60% androstenedione (A), and 20% dehydroepiandrosterone (DHEA). The adrenal produces 25% plasma T, 40% androstenedione, 90% DHEA, and 95% DHEA-sulphate.<sup>11</sup>

In premenopausal women, the ovary secretes 95% of the E2 that enters circulation.<sup>10</sup> After menopause, the ovary virtually stops producing estradiol. Estrone (E1), a weaker estrogen, becomes the predominant circulating estrogen and arises from peripheral conversion of androstenedione.<sup>11</sup> Testosterone levels may either decrease, remain unchanged, or may actually

increase for a few years following menopause due to ovarian stromal hyperplasia. Increased T secretions from the ovarian stroma can occur under the influence of the increased luteinizing hormone levels found in postmenopausal women.<sup>12</sup> This increase in ovarian T is time limited, however, and T levels decrease in all women by the fourth or fifth menopausal year.<sup>12</sup> This short-lived T increase during the peri- and immediate postmenopausal period could possibly explain why women during this stage do not appear to suffer from any particular deficit in sexual desire, response, or satisfaction.<sup>13</sup>

### ROLE OF ESTROGEN

Estrogen is produced in adult quantities by the ovaries by the time a female reaches puberty, and is responsible for the maturation, maintenance, and functioning of the female genitalia. Estrogen also maintains integrity of female secondary sexual characteristics. In addition, estrogen, along with progesterone, govern the female reproductive functions of ovulation, menstruation, gestation, and parturition.<sup>4</sup>

Because the integrity of female genitalia is dependent on estrogen, atrophic changes in these structures ensue when estrogen decreases after menopause.<sup>14</sup> The vaginal epithelium becomes attenuated and pale due to a decrease in vascularity. Marked atrophic changes may result in atrophic vaginitis causing the vaginal epithelium to become thin, inflamed, or even ulcerated.<sup>14</sup> Under these circumstances, coitus becomes extremely painful resulting in loss of libido and decreased desire for sexual intercourse.<sup>4</sup>

It only makes sense that providing relief of dyspareunia is an essential first step in management of postmenopausal desire problems. Estrogen replacement therapy can improve the elasticity, moisture, and thickness of vaginal, perineal, and peri-urethral tissues, thus ameliorating symptoms of vaginal dryness, dyspareunia, and urinary urgency.<sup>15</sup> Further, estrogen replacement is used to alleviate vasomotor symptoms and mood alterations associated with decreased hormone levels perimenopausally.<sup>15</sup> However, numerous studies have suggested that estrogen has no effect on arousal, desire, or libido.<sup>16,17</sup>

In addition to its menopausal benefits, estrogen replacement is recommended for prevention and treatment of osteoporosis and improvement of cardiovascular health, subsequently lowering the risk of myocardial infarctions and strokes.<sup>18</sup> The weight

of evidence suggests that starting hormone replacement therapy (estrogen alone or in combination with progesterone or a progestin) should be a standard of care in postmenopausal females who do not have a contraindication to estrogen supplementation.

### ROLE OF DHEA

There have been multiple documented beneficial effects on endocrine-metabolic parameters of DHEA in animals from enhancing immunoprotective functions to reducing carcinogenesis.<sup>19</sup> The extrapolation of results obtained from animal models to humans is controversial, as animals do not undergo depletion of DHEA over their lifespan as humans do. In addition, doses used in animal studies produce far greater levels of DHEA than those seen in the normal circulation of humans.<sup>20</sup>

Nestler et al reported that oral administration of DHEA at 1600mg/day for 28 days to young (22-25yr) non-obese men resulted in lowering of cholesterol and LDL and decrease in body fat.<sup>21</sup> A similar study done by Mortola giving 1600mg/day of DHEA for 28 days to six obese postmenopausal women resulted in high circulating levels of all androgens with a significant decline in total and HDL cholesterol while LDL remained unchanged. Moreover, insulin resistance was induced by the treatment.<sup>19</sup>

Another study done by Morales et al administered a lower dose of 50mg DHEA for six months to 40- to 70-year old men and women. The 50mg dose of DHEA restored these patients to levels of DHEA found in young adults within two weeks of replacement and were sustained throughout three months. These results noted HDL levels to decline slightly in women with no other lipid change for either gender. Insulin sensitivity and percent body fat were unaltered, but significant increase in bioavailability of Insulin-like growth factor (IGF-I) levels were associated with notable increase in perceived physical and psychological well-being for both men (67%) and women (84%) with no reported change in libido.<sup>22</sup>

A French study by Berr et al followed DHEA levels in patients over four years and confirmed that DHEA levels decrease with age, more in men than women, and found no relationship between global cognitive function and dementia over those four years.<sup>23</sup>

A recent two-week study by Wolf et al concluded that DHEA does not increase cognitive performance and well-being in elderly men and women.<sup>24</sup> Even though it was a large study group, the subjects were

only studied for two weeks, perhaps suggesting that a two-week treatment with DHEA does not seem sufficient to enhance IGF-I, as DHEA achieves its effects on IGF-I through indirect mechanisms, which may take more than two weeks to develop.

Therefore, DHEA does decrease with age in men more than women. Oral doses greater than 50mg/day may lead to androgenization in women. When taken for more than three months, there is an increase in bioavailability of IGF-I by indirect mechanisms that provide perceived increase in physical and psychological well-being with no change in global cognitive function and libido. While DHEA has not been shown to directly change libido, it improves overall feelings of well-being which impact greatly on the sense of sexual satisfaction when given parenterally rather than orally. More investigation is needed in this area.

### ROLE OF TESTOSTERONE

The positive effects of testosterone on female libido were reported as early as 1959 when Waxenberg and his colleagues reported that T deficiency in women produces a marked decrease in libido and sexual responsiveness.<sup>25,26</sup> In 1963, Salmon and Geist proposed that androgens had a three-fold action on female sexuality: 1) Increases susceptibility to psycho-sexual stimulation; 2) Increases the sensitivity of the external genitalia; 3) Increases the intensity of sexual gratification.<sup>27</sup>

Work done by Everitt and Herbert on female Rhesus monkeys suggests that sexual receptivity is controlled by the androgens in the anterior hypothalamus.<sup>8</sup> In previous studies by the same group, the Rhesus monkey underwent bilateral ovariectomy and adrenalectomy, thus removing the source of androgens. These monkeys became sexually unreceptive despite estrogen replacement. Receptivity was restored by injecting T subcutaneously. Injections of DHEA, cortisol, and progesterone were ineffective in restoring receptivity.<sup>28,29</sup> This study lends support that estrogens, progesterone, and DHEA have no effects on libido, yet T appears to affect libido by possibly modulating receptors in the brain.

More recently, Rubinow and Schmidt reported that in men, androgen dependence takes the form of a threshold level, below which libido and sexual function are impaired and above which they are not impaired. There is no correlation between either the ideational or erectile components of sexual function and T in the normal

range.<sup>30</sup> This study theorizes that only when a person's T dips below a "critical level" that sexual functioning is affected and the administration of T can be expected to have beneficial effects.<sup>4,30</sup> There is no reason to believe that these psychophysiological correlates should be any different for women.<sup>4</sup> Therefore the relative minor fluctuations in normal T levels that occur in young, normal cycling females would be of little clinical significance.<sup>4</sup>

Bancroft et al investigated the relationship between T and sexuality in oral contraceptive (OC) using women. OC users complaining of loss of sexual desire or enjoyment (which these women attributed to OC use) were compared with women without sexual problems using the same OCs. The two groups had very similar T levels but the problem group did not benefit from exogenous T administration<sup>31</sup> suggesting that psychosexual problems may serve to obscure testosterone-behavior relationships in young women.<sup>32</sup>

Another study done by Udry et al on females around the age of puberty found that T levels predicted their levels of sexual interest or libido, however sexual activity (coitus) was much more dependent on other psychosocial factors like peer group influences.<sup>33</sup>

A more recent study done by Bancroft et al investigated relationships between free T and measures of sexual attitude and behavior in OCP vs. non OCP users. Results showed that OCP users had an increase in free T with more interest in sexual stimuli and sexual motivation but the non-OCP women in the study had the opposite effect.<sup>32</sup> These results again point to the role of psychosocial factors influencing young women's sexual desire more than T. Furthermore, Kaplan and Owett strongly suggest that if the lack of sexual desire does not occur in ALL situations, then the

complaints of decreased libido are not due to decreased T, rather the result of other psychosocial, environmental, and behavioral factors that need evaluation and counseling. Giving T will be of little or no benefit in these cases.<sup>4</sup>

### SURGICAL MENOPAUSE

The critical role of T in sexual motivation becomes most visible when there is a genuine deficit as in surgical menopause. The fact that women are deprived of ovarian estrogen and T production within 24 to 48 hours of a total hysterectomy and bilateral salpingo-oophorectomy (BSO) has provided a rationale for administering both estrogen and T as replacement therapy.<sup>3</sup>

A study done in Switzerland by Sinclair recruited women suffering from severe loss of libido despite HRT that adequately relieved symptoms such as hot flashes and vaginal dryness. The women were divided into two groups: either receiving estradiol 40mg or combined subcutaneous estradiol 40mg + T 50mg implants. After six weeks, women with combined implants reported an increase in libido and satisfaction of treatment, while libido remained low in the E2 only implant group.<sup>34</sup>

Sherwin et al has extensively studied the effects of surgical menopause on mood, cognition, and libido.<sup>12,35-38</sup> In two prospective studies, she reported that sexual desire, sexual arousal, and number of sexual fantasies were increased in oophorectomized women receiving T or T plus estrogen as compared to women receiving estrogen alone or placebo.<sup>12,35</sup> Sherwin also reports that replacement of estrogen and T in the surgically menopausal woman has been reported to improve cognitive functioning, as well as reduce depression scores, as compared to placebo.<sup>36-38</sup>

Young et al demonstrated that giving oral esterified estrogen 1.25mg in combination with 2.5mg methyltestosterone significantly improved sexual drive and sexual satisfaction following oophorectomy.<sup>39</sup>

There is much compelling evidence that the addition of T to an estrogen replacement regimen is associated with an

enhancement of sexual desire, interest, and enjoyment of sex in postmenopausal women.<sup>3</sup>

### NATURAL MENOPAUSE

The desire for intimacy, affection, and love does not end at any age.<sup>40</sup> When serum hormone levels were measured in a group of postmenopausal women, those women with a higher free T level were more consistently associated with an increased sexual desire.<sup>41</sup> Unfortunately, T levels slowly drop each year after menopause, usually with significant decline of T by the fourth or fifth postmenopausal year.<sup>12</sup>

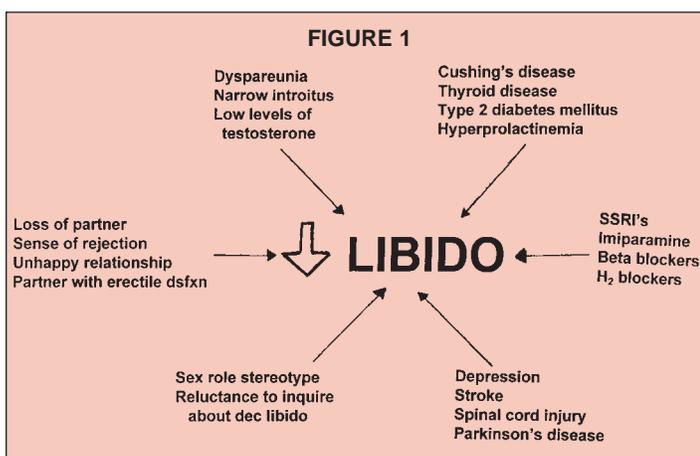
Narrowing of the introitus, which also occurs in menopause, can also induce dyspareunia in women who have intercourse infrequently. Regular sexual activity, including masturbation, also helps to retain normal function.<sup>42</sup>

There are many other factors that can alter libido in women as they age. Diseases like thyroid disorder, Type 2 diabetes, hyperprolactinemia, Cushing's syndrome, and spinal cord injury may all be associated with impaired sexual function.<sup>1</sup> Medications such as imipramine may impair orgasmic response, Serotonin reuptake inhibitors (Prozac®, Paxil®, etc.) have also been associated with decreased libido as well as anorgasmia. Beta blockers and H2 blockers may also diminish libido.<sup>43</sup>

Although menopause itself doesn't increase the occurrence of depression, a variety of illnesses such as Parkinson's disease and stroke, or a chronic illness can be associated with depression.<sup>44</sup> Depression may result from a lack of sexual activity (partner with erectile dysfunction, sense of rejection by partner), or if the woman is "locked" into an unhappy relationship. The loss of a partner and the paucity of older men or other available partners may also result in withdrawal from sexual activity.<sup>1</sup>

Social barriers may further inhibit women from pursuing sexual satisfaction. Western culture is still coming to terms with the fact that sexual behavior continues into old age.<sup>45</sup> Sex role stereotypes that characterize men as sexually aggressive and women as passive are unchanging and probably serve to limit sexual behavior of older women.<sup>3</sup> (Figure 1)

Finally, there are still many physicians who are reluctant to inquire about libido in postmenopausal women. Of those who do inquire, many are hesitant to prescribe T for their female patients. This may be a



reflection of valid concerns about potential virilizing effects.<sup>4</sup> Studies by Sherwin noted that side effects such as hirsutism were dose-dependent. Twenty percent of women who received 150mg testosterone enanthate intramuscularly every four weeks along with estrogen developed hirsutism, but when the dose was reduced to 75mg, less than 5% had increased hair growth.<sup>46</sup> Fortunately, the relatively low levels of T that effectively restore and maintain female libido do not generally result in virilization.<sup>47</sup> Furthermore, T has insignificant effects on lipids and no effects on hepatic function or gamma-glutamyl transferase.<sup>46</sup>

## CONCLUSION

Even though studies on the positive effects of T on libido in postmenopausal women have been accumulating for over 20 years, it is still not standard of care to use, unlike HRT or estrogen replacement. DHEA still needs further investigation but may have secondary effects on well-being that could certainly impact on increasing libido.

This paper suggests that since androgen dependence takes the form of a threshold level in men, it is possible that the same effect applies for women. Therefore, below normal or absent levels of T in women result in loss of libido, but when T levels are normal, other psychosocial, environmental, and behavioral factors influence libido.

All women who have undergone surgical menopause should be questioned for sexual functioning, and T plus estrogen should be considered if they complain of decreased libido. Dual treatment should be considered in menopausal women after their fourth or fifth decade who complain of decreased libido after other psychosocial and environmental factors have been addressed or evaluated. In premenopausal and perimenopausal women complaining of loss of libido, other psychosocial factors are more likely the underlying cause rather than hormonal loss and need to be evaluated.

Testosterone replacement for women has been a neglected area of medicine. Physicians must become more accustomed to discussing sexual issues with patients because therapy for many of their problems is available. The quest for maximizing quality of life, in which sex and sexuality play so important a role, is one that does not end at any age.

## REFERENCES

1. Kaiser J. Sexuality. In Duthie, EH (ed). *Practice of Geriatrics*. Philadelphia, W.B. Saunders. 1998;6:48-56.
2. Kaiser FE. Sexuality in later life. *Clin Geriatr*

*Med*. 1991;7:63-72.

3. Sherwin BB. The psychoendocrinology of aging and female sexuality. *Ann Rev Sex Res*. 1991;2:181-198.
4. Kaplan HS, Owett T. The female androgen deficiency syndrome. *J Sex and Marital Therapy*. 1993;19:3-24.
5. Graziottin A. Hormones and libido. In: Wren BG (ed). *Progress in the Management of the Menopause*. New York, Parthenon Publishing Group. 1996;56:393-400.
6. Riley AJ, Riley EJ, Brown P. Biological aspects of sexual desire in women. *Sex Marital Ther*. 1986;1:35-42.
7. McEwen BS. The brain as a target organ of endocrine hormones. In: Kreiger DT, Hughes JS (eds). *Neuroendocrinol*. Sunderland, MA, Sinauer Assoc. 1980;33-42.
8. Everitt BJ, Herbert J. The effects of implanting testosterone propionate in the central nervous system on the sexual behavior of adrenalectomized female rhesus monkeys. *Brain Res*. 1975;86:109-120.
9. Downes EGR. Sexuality of the menopausal woman. *Brit J Hosp Med*. 1992;47:409-410.
10. Lipsett MB. Steroid hormones. In: Yen SSC, Jaffe RB (eds). *Reproductive Endocrinology, Physiology, Pathophysiology and Clinical Management*. Philadelphia, W.B. Saunders. 1986;140-153.
11. Longcope C. Metabolic clearance and blood production rates of estrogen in postmenopausal women. *Am J Obstetrics and Gynecology*. 1981;111:779-785.
12. Sherwin BB, Gelfand MM. The role of androgen in the maintenance of sexual functioning in oophorectomized women. *Psychosom Med*. 1987;49:397-409.
13. Cutler WB, Garcia CR, McCoy N. Perimenopausal sexuality. *Arc Sex Behav*. 1987;15:225-234.
14. Bergman A, Brenner PF. Alterations in the urogenital system. In: Mishell DR (ed). *Menopause: Physiology and Pharmacology*. Chicago, Year Book Medical Publishers Inc. 1987;67-75.
15. Evans MP, Fleming KC, Evans JM. Hormone replacement therapy: management of common problems. *Mayo Clin Proceedings*. 1995;70:800-805.
16. Campbell S, Whitehead M. Oestrogen therapy and the menopausal syndrome. *Clin Obstet Gynaecol*. 1977;42:31-47.
17. Coope J. Double-blind cross-over study of estrogen replacement. In: Campbell S (ed). *The Management of the Menopause and Post-Menopausal Years*. Baltimore, MD, University Park Press. 1976;159-168.
18. Greendale GA, Judd HL. The menopause: health implications and clinical management. *J Am Geriatr Soc*. 1993;41:426-436.
19. Mortola JF, Yen SSC. The effects of oral dehydroepiandrosterone on endocrine-metabolic parameters in postmenopausal women. *J Clin Endocrinol Metab*. 1990;71:696-704.
20. Kuritzky L. DHEA: Science or wishful thinking? *Hospital Practice*. 1998;85-86, 92.
21. Nestler JE, Barlacini CO, Clore JN, Blackard WG. Dehydroepiandrosterone reduces serum low density lipoprotein levels and body fat but does not alter insulin sensitivity in normal men. *J Clin Endocrinol Metab*. 1972;66:57-61.
22. Morales AJ, Nolan JJ, Nelson JC, Yen SSC. Effects of replacement dose of dehydroepiandrosterone in men and women of advancing age. *J Clin Endocrinol Metab*. 1994;78:1360-1367.
23. Berr C, Lafont S, Debuire B, Dartigues J, Baulieu E. Relationships of dehydroepiandrosterone sulfate in the elderly with functional, psychological, and mental status, and short-term mortality: a French community-based study. *Proc Natl Acad Sci*. 1996;93:13410-13415.
24. Wolf OT, Neumann O, Hellhammer DH, Geiben AC, Strasburger CJ, et al. Effects of a two-week physiological dehydroepiandrosterone substitution on

cognitive performance and well-being in healthy elderly women and men. *J Clin Endocrinol Metab*. 1997;82:2363-2367.

25. Waxenberg SE, Drellick NG, Sutherland AN. The role of hormones in human behavior I: changes in female sexuality after adrenalectomy. *J Clin Endocrin*. 1959;19:193-197.
26. Waxenberg SE, Finkbinder JA, Drellick NG, Sutherland AN. The role of hormones in human behavior II: changes in sexual behavior in relation to vaginal smears of breast-cancer patients after oophorectomy and adrenalectomy. *Psychosom Med*. 1960;22:435-439.
27. Salmon UJ, Geist SH. Affect of androgens upon libido in women. *J Clin Endocrin*. 1963;3:235-238.
28. Everitt BJ, Herbert J. The effects of dexamethasone and androgens on sexual receptivity of female rhesus monkeys. *J Endocrin*. 1971;51:575-588.
29. Everitt BJ, Herbert J, Hamer JD. Sexual receptivity of bilaterally adrenalectomized female rhesus monkeys. *Physiol Behav*. 1972;8:409-415.
30. Rubinow DR, Schmidt PJ. Androgens, brain, and behavior. *Am J Psychiatry*. 1996;153:974-984.
31. Bancroft J, Davidson DW, Warner P, Tyrer G. Androgens and sexual behavior in women using oral contraceptives. *Clin Endocrinol*. 1980;12:327-340.
32. Bancroft J, Sherwin BB, Alexander GM, Davidson DW, Walker A. Oral contraceptives, androgens, and the sexuality of young women: the role of androgens. *Arc Sex Behav*. 1991;20:121-135.
33. Udry JR, Talbert LM, Morris NM. Biosocial foundations for adolescent female sexuality. *Demography*. 1986;23:217-230.
34. Sinclair ME, Suter PM. Effect of combined implants of oestradiol and testosterone on libido in postmenopausal women. *BMJ*. 1987;294:936-937.
35. Sherwin BB, Gelfand MM, Brender W. Androgen enhances sexual motivation in females; a prospective crossover study of sex steroid administration in the surgical menopause. *Psychosom Med*. 1985;47:339-351.
36. Sherwin BB, Gelfand MM. Sex steroids and affect in the surgical menopause: a double blind, crossover study. *Psychoneuroendocrinol*. 1985;10:325-335.
37. Sherwin BB. Affective changes with estrogen and androgen replacement therapy in surgically menopausal women. *J Aff Disord*. 1988;14:177-187.
38. Sherwin BB. Estrogen and/or androgen replacement therapy and cognitive functioning in surgically menopausal women. *Psychoneuroendocrinol*. 1988;13:345-357.
39. Young R, Wiita B, Dobbs J, Downey L. Comparison of estrogen plus androgen and estrogen on libido and sexual satisfaction in recently oophorectomized women. Abstract, presented at the 1992 North American Menopausal Society Meeting.
40. Bretschneider JG, McCoy NL. Sexual interest and behavior in healthy 80 to 102 year olds. *Arch Sex Behav*. 1988;17:109-129.
41. Bachmann GA, Leiblum SR. Sexuality in sexagenarian women. *Maturitas*. 1991;13:43-50.
42. Ringel M. Beyond hormones: other treatments for menopausal symptoms. *Patient Care*. 1998;28-54.
43. Anonymous. Drugs that cause sexual dysfunction: an update. *Med Letter*. 1992;34:73-78.
44. Musetti L, Perugi G, Soriani A, et al. Depression before and after age 65: a re-examination. *Br J Psychiatry*. 1989;155:330-336.
45. Covey HC. Perceptions and attitudes toward sexuality of the elderly during the middle ages. *Gerontologist*. 1989;29:93-100.
46. Sherwin BB. The use of androgens in the postmenopause: evidence from clinical studies. In: Wren BG (ed). *Progress in the Management of Menopause*. New York, Parthenon Publishing Group. 1996;262-266.
47. Sherwin BB. Aging and sexuality: a biopsychoso-

# Consumer Ambivalence and the Role of the Physician in Counseling



**Alessandra Graziottin,  
M.D.**

Gynecologist-Sexologist,  
Director of the Menopause  
Center, H. San Raffaele  
Resnati, Milano, Italy,  
Board of the Italian  
Menopause Society

## INTRODUCTION

Medicine has two main domains of intervention: curative and preventive. This is particularly true for the menopausal woman. Indications to hormonal replacement therapy (HRT) after the menopause are two-fold: 1) for relief of post-menopausal symptoms secondary to estrogen deficiency (curative intervention); 2) for reduction in risk of diseases associated with estrogen deficiency (preventive intervention).<sup>1,2</sup> This basic difference involves a different decision-making process, usually overlooked in the ongoing discussions about compliance to HRT.<sup>2</sup> In the curative domain, the therapeutic decision relies mostly on the physician. The woman is dependent on his/her curative decision, the asymmetry of the relationship and communication increasing with the seriousness of the disease and its acuteness, with an up-down direction of prescription and recommendations. In the preventive domain, the decision is increasingly shared with the woman. The woman intensely feels the responsibility for choosing the best for her life and health, the more indeed when she is asked to ingest hormones daily to prevent remote diseases and, hopefully, to improve her present quality of life. She therefore needs a more symmetric relationship, open to questions, doubts, expressions of fears and concerns, and is more troubled by potential long term-side effects of this treatment. Coherently with this difference, compliance to treatment is easier to obtain in symptomatic patients, when the efficacy in relieving disturbances is a major factor in treatment satisfaction for the usual short period of time when HRT is

needed.<sup>2</sup> Major problems in compliance arise for the preventive indication, when, in absence of symptoms, all the decisions will rely not on REAL benefits and risks but on a proper PERCEPTION of benefits and risks.<sup>1</sup> Perception is a key mental step, as it highlights the SUBJECTIVE involvement in the decision-making process and the many CONFLICTING emotional and cognitive factors that may distort the process itself.<sup>2</sup> Focusing therefore on the mental processes that lead to HRT one may recognize three main steps: decision-making process ("thinking about HRT and asking a doctor about it"); motivation to start HRT (decision-making process wavers in favor of starting HRT); and compliance with HRT (satisfaction of use leads to continuation). All these steps are critical and more dependent on the woman's attitude in the preventive domain, where conflicting decisional factors may determine the final judgment.

## THE CONCEPT OF "AMBIVALENCE"

From the psychodynamic point of view, this conflicting attitude in the decision-making process and human behavior, i.e., the coexistence of conflicting fears and desires, is called "ambivalence."<sup>3</sup> Ambivalence is a familiar feeling, as all human beings experience it, mostly in decision-making processes with high emotional content. It has a particular interest in preventive medicine, when one is expected to use a prophylactic pharmacologic treatment for years, in order to avoid some unwanted and/or potentially life threatening problems. It is a critical variable in accepting HRT after the menopause, as "hormone" (SEXUAL hormone, in fact) is a potent evocative word, coagulating fears and adverse attitudes. Ambivalence is therefore one of the most powerful and yet poorly recognized psychodynamic factors that may affect the decision-making process toward HRT, the motivation to start it, and the compliance with it.

Because HRT only provides supplementation or replacement of deficient ovarian hormones, the most important medical benefits of HRT may require continued administration for an extended, indefinitely long period of time and may even require lifelong administration. Motivation to continue HRT over the years, and compliance with it, must therefore be addressed in a serious way if we are to have any hope of realizing the full impact of HRT.<sup>1</sup> Ambivalence is one of the critical factors to be

understood and properly managed, if this goal is to be achieved.

## AMBIVALENCE TOWARD HRT

Ambivalence (and concerns) may interest: COGNITION, when one expresses an idea and its contrary at the same time; WILL, when one is willing and not willing to do something at the same time; AFFECTION, i.e., when one feels conflicting emotional states, say fears and desires, love and hate, or sympathy and aversion at the same time.<sup>3</sup> All these aspects may be present in request or avoidance, motivation, and compliance dynamics to HRT, affecting consumer ambivalence toward treatment.

Ambivalence toward HRT may be "spontaneous" in the woman, when it is an expression of a "natural" attitude toward life's seasons and indicates the reluctance or frank aversion to use "drugs" to modify the natural process of aging. It may be "mediagenic" (the word is coined by the author) when pros and cons of HRT are reported in TV and radio comments, newspapers, and magazines, with a strong emotional involvement, more influenced by ideological backgrounds than scientific data. This source of ambivalence is critical, as the majority of women get their information on HRT from the media.<sup>4</sup> In mediagenic ambivalence, fears, focused on breast cancer, are usually emphasized with a parallel dismissal of the many benefits well-prescribed HRT may give. On the opposite front, the media could encourage unrealistic expectations from HRT, especially when they present it as a way to "regain youth" or to feel new again.<sup>2</sup>

Ambivalence may also be "iatrogenic." This is one of the strongest and most insidious causes of ambivalence and, consequently, of poor compliance in women. The "iatrogenic" ambivalence has two main sources. It may be triggered by the individual doctor, who prescribes HRT with verbal and/or non-verbal comments that may worry the woman. This "ambivalent" prescription could be partially responsible for the non-compliance to the prescription itself.<sup>6</sup> In one large survey, 20% to 30% of patients given a prescription for HRT never had the prescription filled; and of those who did, 10% took their medications sporadically and 20% stopped therapy within nine months of starting.<sup>6</sup> The second iatrogenic cause of ambivalence is the reported conflicting attitude between different physicians toward HRT, reported by 47% of women who dropped out of the treatment.<sup>7</sup> On the contrary, when the atti-

tude of doctors is clear and positive, the adequacy of counseling becomes a major factor in compliance.<sup>1,4,8</sup> Different sources of ambivalence usually overlap in the individual woman, making difficult both the decision to start and the motivation to stay on treatment, even in light of minor side-effects that may become major causes of drop-out.<sup>9</sup>

Ambivalence toward HRT arises from two main conflicting areas: fears and desires associated with sexual hormones. Most frequent fears involve: cancer,<sup>1,4-7</sup> weight gain,<sup>1,4,7</sup> feeling unnatural<sup>7</sup> or medicalized, return of menses,<sup>1,4,5,7</sup> headaches or premenstrual syndrome (PMS).<sup>7</sup> These fears are usually so potent that they may explain the reduced number of women who start HRT and the very few who stay on treatment for more than one year.<sup>1,4-8</sup> These potent drawbacks are now faced by the growing knowledge that women can positively affect the quality of aging and that HRT can improve it a great deal. The increasing number of women asking for HRT in recent years is positively motivated by the desire for better physical health, improving emotional well-being, having a better self-image, feeling empowered and in control of the aging process, improving memory, and improving sexual satisfaction.<sup>4-8</sup> Sexuality is openly raised in the consultation only in a minority of cases, usually when coital pain (dyspareunia) is disturbing for the patient. It is recognized to be an important end-point of the treatment if the woman feels she is listened to by an understanding doctor who is able to ease the feelings of guilt, shame, and uneasiness women have when they openly raise sexual issues in the clinical consultation.<sup>10</sup> Negative feelings are more intense in the postmenopausal years when sexuality is still considered a taboo subject.

The final decision toward HRT depends on the balance of these two groups of factors. When the conflict is strong because both fears and desires are emotionally potent, the psychodynamic end result may be a paralyzing effect on the decision-making process. The woman will not ask for HRT or will not comply to it.<sup>2,6</sup>

## THE ROLE OF THE PHYSICIAN IN COUNSELING

Preventive medicine requires a different attitude in the physician, who should be able to adapt to the increasing demand of dialogue in the first two steps of the decision-making process. Because of the per-

ceptive basis and the conflicting nature they are made of, consumer ambivalence needs to be managed with two main focuses in mind:

### 1) FOCUS ON COMMUNICATION

Quality of communication (and counseling) is critical in medicine and in all human experiences where fear is high.<sup>1,6-9</sup>

To reduce fears and the “infectious anxiety” they may convey,<sup>2</sup> critical steps are:

- listen carefully to fears and expectations, paying attention to verbal and non-verbal language (the latter has the highest impact on the emotional perception of the counseling);<sup>11</sup> speak simply, as cognitive difficulties reinforce the feeling of being manipulated, misunderstood, or not “listened to.”<sup>7</sup>
- address fears properly. Precise answers have the highest reassuring effect and help the patient to perceive herself as an active part of the decision-making process. If the woman is afraid of weight gain, start the answer with the caring sentence: “I understand your concern (stressing “understand”) and I will help you in maintaining your weight control.” That sympathetic opening will immediately create a bridge of trust and confidence, and will improve the alliance between doctor and patient.<sup>9</sup> Then detail what is important in weight control: physical activity first, then quality of diet, last HRT.
- transform expectations or desires into motivation to HRT: this is an easy and yet poorly utilized communicative medical strategy. Doctors should be flexible and not focus on osteoporosis, for example, if the patient’s major concern is memory loss or worsening of the skin. The more the patient understands that her expectations will be met, the more she will be compliant. The other benefits of HRT will come as “fringe benefits” of the treatment for her major concern. A treatment centered on the patient’s needs has the highest probability of compliance over time.<sup>12,13</sup>
- give time to think about HRT. Ambivalence, because of its conflicting nature, requires time to get through. To “force” the woman’s decision will only end in a patient leaving the doctor’s office with a prescription and never filling it. Usually, a first counseling clarifies the hottest issues; a second one may be useful and sometimes essential to reinforce motivation and definitely alleviate fears, leading to a really motivated start of the treatment.<sup>2,13</sup>
- find time for the consultation about HRT. The complex decision-making process involved in HRT requires dedicated doc-

tors, willing not only to listen and communicate, but also to increase the length of time for each consultation. Time is a critical, independent variable in the quality of doctor-patient communication. It is easier to find in private practice, where quality of consultation may be preferred to the crude numbers. It is more difficult to be respected in public hospitals pressured by multiple medical activities. Dedicated, well-trained junior doctors, with a supervising senior for difficult cases, could be a positive answer, combining “curing and caring” attitudes for the patient, and quality of training for the doctors in a field where doctor-patient communication is an increasing and yet overlooked value. Educational booklets and women’s group discussions may be helpful in addressing the most frequent ambivalence, fears and concerns, and answering the most frequent questions.

### 2) FOCUS ON CONTENT OF FEARS

To be effective, reassurance should be convincing along with facts and figures quoted on every single concern. Critical steps include:

- never dismiss fears as banal or trivial. If the patient is clearly concerned about HRT, the physician should raise the critical question: “What are you afraid of?” Fears are dominating the decision-making process of the patient and this is the first very good reason why they should be addressed properly. They also clarify patient’s priorities and help the understanding doctor to tailor both motivation and treatment on the individual’s needs.<sup>2,9</sup>
- address fears directly and specifically; counterbalance medical fears against medical advantages. If the woman is afraid of breast cancer, the answer should be focused on this point. First, analyze the patient family history, with a pertinent comment on the actual risk. Second, tell her that the risk is moderately increased after eight years of treatment, and more for “in situ” cancers than invasive. Critical attention should be used in referring to the concept of relative risk (RR): for example, RR of 1.2 means there is 20% increased risk among women exposed to risk of breast cancer, and not 20% more of 100; i.e., if the average risk is that 10 women in 100 will develop breast cancer during their lifetime, a RR of 1.2 means that two more in 100 could develop it after more than five to eight years exposure to HRT. This cancer is usually diagnosed early, thanks to the periodic mammography, is more differenti-

ated, less invasive, and more curable in the majority of cases.<sup>9,14</sup> In women without a family risk of breast cancer, this risk is well balanced by the many advantages: first, on the same oncological field, as HRT reduces colon/rectal cancer by 15% to 20% (if she has a family risk for this kind of cancer, this advantage should be stressed even more); and second, pertaining to cardiovascular risk, osteoporosis, urogenital symptoms, Alzheimer's disease, and sexuality. Family and personal risks should be weighed against the breast cancer risk, so that the woman will participate in the judgment the doctor is making, feeling at the same time understood and reassured in concrete words.

- if fear of headache or of premenstrual syndrome symptoms (PMS) is the issue, say that you understand the concern and will try to prevent this unpleasant "return" of negative effects with three lines of interventions: first, by starting with low doses, increasing them to reach the lowest effective dose; second, by prescribing continuous estrogenic treatment (only in the hysterectomized woman; either continuous combined or continuous sequential if she has the uterus), as catamenial headache and/or PMS seem to be triggered by estrogen fluctuations; third, by prescribing patches, which seem to guarantee optimal plasmatic constant levels.<sup>9</sup>
- distinguish emotional concerns from medical ones.

These apparently obvious recommendations are usually overlooked in clinical practice, where the counseling fluctuates from one mental domain to another, with substantial dismissal of emotional issues that are critical in the final decision-making process, as fears have the last word.<sup>2,12,13,16</sup>

### WHO COUNSELS WHO? MANAGEMENT OF IATROGENIC AMBIVALENCE

Physicians' attitudes toward whatever treatment are critical factors in determining success or failure of it. When ambivalence toward HRT (or whatever treatment) is strong in the physician, it will pervade the consultation, causing a distortion in the information and affecting the whole quality of counseling.<sup>13</sup>

Following are guidelines on avoiding unconscious negative dynamics:

- listen to your inner attitude toward HRT and menopausal patients. The first point is critical from the scientific point of view, as

the core of ambivalence is the uncertainty on potential cancer increase, particularly breast cancer, because of HRT. The second is human, and relies on the personal attitude to doctor-patient relationship. Some doctors may be excellent surgeons or obstetricians, but may be impatient with menopausal women and all their complaints and their need to discuss everything. Some physicians may lack the patience required in tailoring treatment and answering many phone calls for "minor" side-effects. Recognizing these negative attitudes should induce a different selection of patients and/or different areas of clinical practice.

- distinguish objective difficulties in management of HRT side-effects from subjective ones. Sometimes breakthrough bleeding or headaches are difficult to manage. It is important to accept that even HRT should be adjusted and the proper answer should not be an irritated "give it up" at the very first problem or side-effect that appears.<sup>9</sup>
- cope with your personal ambivalences toward HRT. Addressing them is a major step in helping patients in their personal decision-making process.
- fears are infectious and are often unconsciously shared between patient and physician. Understanding this silent colluding process is another major step in a confident and successful doctor-patient relationship.<sup>2,9</sup>

### MANAGEMENT OF MEDIAGENIC AMBIVALENCE TOWARD HRT

To clarify the scenario, urgent, clear information on HRT is needed. Critical attention should be used in referring to the concept of relative risk (RR) that is too often reported in terms of absolute figures. This deplorable mistake causes a dramatic increase of social fears and phantasms toward HRT, particularly when breast cancer is the issue.<sup>2,4,5,14</sup> Avoidance of "sensational" reporting and a rigorous ethic of doctor's interaction with the media are essential if it is to become an informative and educational ally and not an enemy to HRT.

### CONCLUSION

In spite of the many advantages HRT guarantees to postmenopausal women in the short- and long-term, only a minority of them comply to treatment for a significant length of time. Ambivalences, the coexistence of fear and desire regarding HRT, are

major psychodynamic factors that may deeply affect the decision-making process toward hormonal treatment, mostly in the preventive domain. Understanding ambivalences, recognizing their different sources, and actively working to get through them are critical steps if we really are willing to give women the concrete chance of a better life in older age. The methodology of clinical consultation in preventive HRT may finally be considered a useful training model to improve medical skills in communication and management of patient and consumer ambivalence in all the other medical fields, thereby improving the overall ability to cure and care, with reciprocal satisfaction of patient and physician.

### REFERENCES

1. Stumpf PG, Trolice MP. Compliance problems with hormone replacement therapy. *Obstet Gynecol Clinics North Am.* 1994;21:2:219-229.
2. Graziottin A. *Management of ambivalences towards HRT.* Proceedings of the 3rd International Symposium on Women's Health in Menopause: risk reduction strategies-improved quality of life. Florence. June 13-16, 1998 (in press).
3. Galimberti U. *Dizionario di psicologia.* Torino. *UTET.* 1992;41-42.
4. Okon MA, Lee S, Li TC. A study to examine women's knowledge, perception and acceptability of hormone replacement therapy. *European Menopausal Journal.* 1996;3:2:47-52.
5. Hammond CB. Women's concerns with hormone replacement therapy. *Fertil Steril.* 1994;62:(suppl.2):6:157S-160S.
6. Ryan PJ, Harrison R, Blake GM. Compliance with hormone replacement therapy (HRT) after screening for postmenopausal osteoporosis. *Br J Obstet Gynaecol.* 1992;99:325-328.
7. Graziottin A. HRT: from motivation to compliance. In: Paoletti R, Grosignani PG, Kenemans P, Samsioe G, Soma M, Jackson AS. Dordrecht, Kluwer Academic Publishers. 1997;263-273.
8. Coope J, Marsh J. Can we improve compliance with long-term HRT? *Maturitas.* 1992;15:151-158.
9. Graziottin A, De Aloysio D. What do women want? What can we give them? In: Birkhauser MH, Rozembaum H (eds). *IV European Congress on Menopause.* Paris, ESKA ed. 1998;195-201.
10. Graziottin A. Sexuality in the elderly. In: Birkhauser MH, Rozembaum H (eds). *IV European Congress on Menopause.* Paris, ESKA ed. 1998;513-520.
11. Bandler R, Grinder J. *Frogs into princesses: neuro-linguistic programming.* Real People Press, New York. 1979.
12. Haley J. *Strategies of psychotherapy.* Grune & Stratton, New York. 1963.
13. Balint M. *The doctor, his patient and the illness.* Pitman Medical Publishing Co. Ltd., London. 1957.
14. Beral V, Reeves G, Bull D, et al. Breast cancer and hormone replacement therapy: putting the risk into context. In: Birkhauser MH, Rozembaum H (eds). *IV European Congress on Menopause.* Paris, ESKA ed. 1998;267-278.
15. Kurzer MS, Xia Xu. Dietary phytoestrogens. *Annu Rev Nutr.* 1997;17:353-381.
16. Gabbard GO. *Psychodynamic psychiatry in clinical practice.* The DSM IV edition. American Psychi-

## In This Issue of Menopausal Medicine

### Estrogen and Alzheimer's Disease: Current Status

page 1

**Victor W. Henderson, M.D., M.S.**

Professor of Neurology, Gerontology, and Psychology,  
University of Southern California, Los Angeles, CA;

Grant Recipient: National Institutes of Health, Alzheimer's Association,  
Wyeth-Ayerst Laboratories, French Foundation for Alzheimer Research;

Consultant: Organon, Procter and Gamble, Lilly Research Laboratories

### Effects of Estrogens and Androgens on the Libido of Women Following Surgical and Natural Menopause

page 5

**Asma A. Weber, M.D.**

Junior Associate Faculty, Department of Family Medicine,  
Eastern Virginia Medical School, Norfolk, VA

### Consumer Ambivalence and the Role of the Physician in Counseling

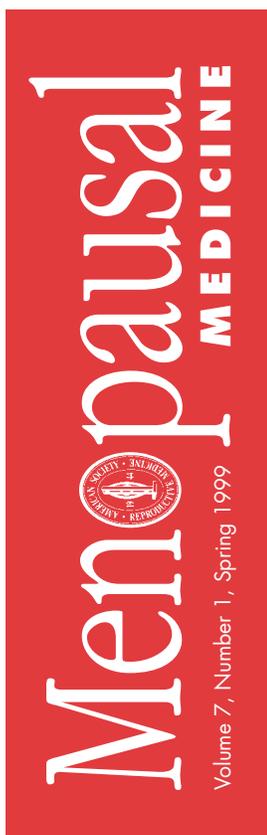
page 9

**Alessandra Graziottin, M.D.**

Gynecologist-Sexologist, Director of the Menopause Center,

AMERICAN SOCIETY FOR  
REPRODUCTIVE MEDICINE  
1209 Montgomery Highway  
Birmingham, Alabama 35216-2809

Non-Profit Org.  
U.S. Postage  
**PAID**  
Permit No. 1547  
Birmingham, AL



H. San Raffaele Resnati, Milano,  
Italy;  
Board of the Italian Menopause  
Society













