

EDITORIAL

It might be wise to consider adding androgen to the estrogen or estrogen-progestin regimens in the appropriate patients

In the world of hormone therapy (HT), estrogen has been prescribed for over 50 years, progestin for over 25 years, and androgen for over 45 years. In the management of perimenopausal, menopausal, and postmenopausal patients, there are certain guidelines for the use of HT. There are acute symptoms, such as vasomotor and atrophic symptoms, and long-term benefits, such as the prevention of osteoporosis and, possibly, bowel cancer. The risks involve the incidence of breast cancer, endometrial cancer, and possible clinical side effects. Presently, cardiovascular disease and senile dementia are being re-evaluated. The Women's Health Initiative (WHI) study,¹ published in July 2002, created a tremendous upset in the risk factor of hormone use, and although the increased risk factor was 8 in 10,000 women-years of breast cancer, the upheaval psychologically and clinically has been very great. The article by Dimitrakakis et al² in this issue of *Menopause* provides important information about the addition of testosterone to the HT regimen. In their evaluation of 508 menopausal women receiving testosterone in addition to the usual HT, the incidence of breast cancer in testosterone users was 238 per 100,000 women, and the rate for estrogen-progestin and testosterone users was 293 women-years. It is substantially less than that for women receiving estrogen-progestin in the WHI study, which was 380 per 100,000 women-years, and in the million-women study, which was 430 per 100,000 women.³ The breast cancer rate in the testosterone users was closest to that reported for HT never users. In the latter, the rate was 283 per 100,000 women-years, and their age standardization rate was the same as for the general population in South Australia.

It has been known since 1950 that androgen (A) when added to estrogen (E) improves libido.^{4,5} The information was anecdotal, and it was not until the mid-1980s that Sherwin and Gelfand⁶⁻⁸ demonstrated that the addition of androgen to estrogen in HT improves

sexuality, energy, and well-being and also augments libido. Many other studies have confirmed this.⁹⁻¹¹

In both males and females, the synthesis of androgens is triggered by hormonal signals from the hypothalamus and the pituitary gland. In women, testosterone (T) is produced by the ovaries and the adrenal glands and by peripheral conversion of precursor hormones. Testosterone can be aromatized to estradiol, the most potent female estrogen, by the aromatase enzyme complex. Only 1% to 2% of total circulating testosterone is free and biologically active. The rest is bound by sex hormone-binding globulin (SHBG) and albumin. Increasing levels of estradiol increase SHBG and decrease testosterone levels, exacerbating T deficiency syndromes.

In a recent Canadian survey, 70.8% of the practitioners stated that they added androgen to estrogen for the enhancement of the quality of life. This is a surprising percentage, considering that 10 years ago probably only 5% of practitioners even knew about androgen-estrogen therapy. In a recent review, the authors¹² concluded that the use of androgens in women has no risk consequences as long as they are used judiciously. Judiciously, in most cases or in every case, means the maintenance of androgen levels within normal limits.

Several studies have documented the positive effects of androgens on bone mineral density in naturally and surgically postmenopausal women.¹³⁻¹⁵ Estrogens and androgens diminish bone resorption and androgens also enhance bone formation. It has also been shown that, 2 to 4 years after women discontinue androgen-estrogen therapy, their bone mass density continues to improve, unlike the situation with women taking estrogen therapy, who upon discontinuing it begin to lose bone mass. These studies offer strong support for the addition of androgen to estrogen HT.

WHI studies indicated that cardiovascular disease could not be an indication for the commencement of

HT. When one adds androgen to the estrogen or estrogen-progestin therapy, it has been shown not to affect the lipid profile adversely¹⁶ and it increases the dilatation of coronary arteries when taken parenterally.^{17,18}

The increase in breast cancer incidence has certainly been a psychological trauma to patients who are on HT, and although the number of women shown to have increased risk is very small, one cannot underestimate the impact on patients, as evidenced by their refusal to take or their desire to discontinue HT. Lovell investigated the effects of parenteral androgen-estrogen therapy on the incidence of breast cancer.¹⁹ He reviewed nearly 4,000 cases of women who had been treated and found that the incidence of breast cancer was lower in the treated group than in the population without treatment. Poulin and Baker described the inhibitory effect of 5 α dihydrotestosterone (DHT) and its precursor testosterone on the growth of the estrogen-sensitive human breast cancer cell line ZR-75-1.²⁰ In the absence of estrogens, cell proliferation was measured after a 12-day incubation period and was 50% to 60% inhibited by maximum concentration of 5 α DHT or androstenedione. The antiproliferative effect of androgens was completely reversed by the antiandrogen hydroxyflutamide, thus indicating an androgen receptor-mediated mechanism. Kellokumpu-Lehtinen et al²¹ compared the risks in response to tamoxifen (TAM) versus nandrolone decanoate (NAN) in previously untreated menopausal women with advanced breast cancer. In the 67 patients treated with TAM, 15% had complete or partial remission, 42% had stabilized disease, and 43% had progressive disease. In the 60 patients treated with NAN the results were 17, 37, and 47 respectively. Dr. Glenn D. Braunstein (Cedars-Sinai Medical Center-UCLA School of Medicine, Los Angeles, CA), who moderated the initial briefing of the presentation of the Dimitrakakis et al² paper (June 2003), said the findings do have a biologic possibility. There have been in vitro studies of breast cancer cell lines that are stimulated by estrogen, which suggest that adding androgens inhibits that stimulation. "These studies do fit in very well with basic science," he said. In Rhesus monkeys, testosterone has been shown to inhibit estrogen's mitogenic effects.

There are numerous ongoing projects, in which testosterone will be delivered by patch,²² by gel, orally, or by injection. In today's appraisal of the quality-of-life aspects involved with the use of HT, the addition of androgen plays a very important and dynamic role. On a very personal level, we have had patients on estrogen-androgen therapy for up to 40 years. Three thousand patients are in this group, and we are in the process of

analyzing the incidence of breast cancer and other possible side effects they might have experienced. It is important for us to state that, in a pilot study of the first 100 women who were on estrogen-androgen therapy for more than 5 years, the incidence of breast cancer in those patients was lower than that in those who were on estrogen or estrogen-progestin. The addition of androgen to the estrogen or estrogen-progestin regimen is here to stay. Judicious evaluation and use is advocated.

Morrie M. Gelfand, CM, MD
McGill University,
Montreal, Quebec, Canada

REFERENCES

- Rossouw JE, Anderson GL, Prentice RL, et al. Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. *JAMA* 2002;288:321-333.
- Dimitrakakis C, Jones RA, Liu A, Bondy CA. Breast cancer incidence in menopausal women using testosterone in addition to usual hormone therapy. *Menopause* 2004;11:xxx-xxx.
- Beral V. Breast cancer and hormone-replacement therapy in the million women study. *The Lancet* 2003;362:419-427.
- Greenblatt RB, Barfield WE, Garner JF, Calk GL, Harrod JP Jr. Evaluation of an estrogen, androgen, estrogen-androgen combination, and a placebo in the treatment of the menopause. *J Clin Endocrinol Metab* 1950;10:1547-1558.
- Grody MH, Lampe EH, Master WH. Estrogen-androgen substitution therapy in the aged female. *Obstet Gynecol* 1953;2:36-45.
- Sherwin BB, Gelfand MM. Sex steroids and affect in the surgical menopause: a double-blind, cross-over study. *Psychoneuroendocrinology* 1985;10:325-335.
- Sherwin BB, Gelfand MM. The role of androgen in the maintenance of sexual functioning in oophorectomized women. *Psychosom Med* 1987;49:397-409.
- Gelfand MM. Estrogen-androgen hormone replacement. In: Swartz DP, ed. *Hormone Replacement Therapy*. Baltimore, MD: Williams & Wilkins, 1992;221-234.
- Davis S. Testosterone and sexual desire in women. *J Sex Edu Ther* 2000;25:25-32.
- Sarrel P, Dobay B, Wiita B. Estrogen and estrogen-androgen replacement in postmenopausal women dissatisfied with estrogen-only therapy: sexual behavior and neuroendocrine responses. *J Reprod Med* 1998;43:847-856.
- Simon JA, Klaiber E. Double-blind comparison of two doses of estrogen and estrogen-androgen therapy in naturally postmenopausal women: neuroendocrine, psychological and psychosomatic effects. *Fertil Steril* 1996;66:S71.
- Gelfand MM, Wiita B. Androgen and estrogen-androgen hormone replacement therapy: a review of the safety literature, 1941 to 1996. *Clin Ther* 1997;19:383-404.
- Raisz LG, Wiita B, Artis A, et al. Comparison of the effects of estrogen alone and estrogen plus androgen on biochemical markers of bone formation and resorption in postmenopausal women. *J Clin Endocrinol Metab* 1996;81:37-43.
- Suevas M, Studd JW. Increase in bone mass after one year of percutaneous estradiol and testosterone implants in postmenopausal women who have previously received long-term oral estrogens. *Br J Obstet Gynecol* 1992;99:757-760.

EDITORIAL

15. Barrett-Connor E, Timmons C. Interim safety analysis of a two-year study comparing oral estrogen-androgen and conjugated estrogens in surgically menopausal women. The Estratest Working Group. *J Womens Health* 1996;5:593–602.
16. Sherwin BB, Gelfand MM, Schucher R, Gabor S. Postmenopausal estrogen and androgen replacement and lipid concentrations. *Am J Obstet Gynecol* 1987;156:414–419.
17. Honoré EK, Williams JK. Methyltestosterone does not diminish the beneficial effects of estrogen replacement therapy on coronary artery reactivity in cynomolgus monkeys. *Menopause* 1996;3:20–26.
18. Worboys S, Kotsopoulos D, Teede H, McGrath B, Davis SR. Evidence that parenteral testosterone therapy may improve endothelium-dependent and -independent vasodilation in postmenopausal women already receiving estrogen. *J Clin Endocrinol Metab* 2001;86:158–161.
19. Lovell CW. Breast cancer incidence with parenteral estradiol and testosterone replacement therapy [Abstract]. *Menopause* 1994;1:150.
20. Poulin R, Baker D, Labrie F. Androgens inhibit basal and estrogen-induced cell proliferation in the ZR-75-1 breast cancer cell line. *Breast Cancer Res Treat* 1988;12:213–225.
21. Kellokumpu-Lehtinen P, Huovinen R, Johansson R. Hormonal treatment of advanced breast cancer: a randomized trial of tamoxifen versus nandrolone decanoate. *Cancer* 1987;60:2376–2381.
22. Shifren JL, Braunstein GD, Simon JA, et al. Transdermal testosterone treatment in women with impaired sexual function after oophorectomy. *N Engl J Med* 2000;343:682–688.