

Androgen deficiency: menopause and estrogen-related factors

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Objective: To describe the changes in ovarian hormones caused by natural menopause and hormone replacement therapy that have effects on androgen bioavailability and to describe indications for androgen replacement in postmenopausal women.

Design: Review of English language-published research over the last 35 years from January 1, 1966 to June 30, 2001 using MEDLINE.

Setting: Academic medical center.

Intervention(s): None.

Result(s): In menopausal women, the effects of estradiol depletion and replacement on sex hormone-binding globulin appear to have clinically significant effects on bioavailable endogenous androgens. Many women whose menopause-related symptoms and bone loss responded inadequately to estrogen replacement were found to benefit from the addition of androgens. Most studies have focused on the sexual benefits of prescribing androgens to postmenopausal women. New studies have begun exploring the effects of androgens in other body systems, including the brain and the cardiovascular system.

Conclusion(s): Estrogen depletion and replacement therapy at menopause can have clinically significant effects on bioavailability of endogenous androgens. Androgens complement the actions of estrogens in symptom control and disease prevention in postmenopausal women. Although androgen effects on sexual function are important, effects of androgens in many body systems should be considered in future research to determine optimal postmenopausal hormone replacement therapy. (Fertil Steril® 2002;77(Suppl 4):S63-7. ©2002 by American Society for Reproductive Medicine.)

Key Words: Menopause, androgens, SHBG, sex, osteoporosis, hot flashes

The natural depletion of oocytes and ovarian follicles that occurs with aging leads to the menopause, the time of the last natural menstrual flow and the end of the biologically reproductive phase of a woman's life. The mean age for menopause is 51 plus or minus 4 years, with >30 years' life expectancy after menopause for women in the developed nations (1). Follicle depletion results in loss of theca and granulosa cells, ovarian cells that respectively produce androgens and estrogens (Es) (2). As a result, serum E₂ declines to a fraction of premenopausal levels, and progesterone levels remain extremely low (3-5).

Throughout a woman's reproductive life, ovaries produce more androgens than Es; serum T levels, expressed in picograms per milliliter, are about 1.5 times the level of E₂ (350 pg/mL vs. 200 pg/mL), as extrapolated from the work of Longcope (6). In addition to their production in ovarian theca cells, ovarian androgens are also produced by ovarian stromal

cells. Decline in ovarian androgen production begins many years before the menopause (6). As a result, women entering their perimenopausal and postmenopausal years do show a decline in serum androgen levels compared with women in their 20s.

However, the rate of decline in production does not appear to be increased at the time of menopause (6). There is evidence that increased stromal cell production of androgens after menopause serves a somewhat compensatory role (7). However, by a decade after the menopause, androgen production has declined so that serum levels of T and androstenedione in women aged 60 years are about half those in women at age 40 years, who in turn have levels significantly below those of the peak levels seen in women in their mid-20s (8).

Ovarian hormones are released into the bloodstream, circulate throughout the body, enter cells in every tissue system, and induce a myriad of cell actions affecting cell structure

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and function. These effects, initially believed to be limited to reproductive function, are now understood to contribute to overall normal physiological response and disease prevention. As a result, when thinking of the implications of ovarian hormone deficiency, it is important to extend considerations beyond sexual and reproductive function and to also include such diverse functions as the circulation of blood, muscle, and bone metabolism, immunologic response, and nervous system activity.

Signs and symptoms of disordered function in almost any of the body's systems could be caused by decreased production of Es, androgens, and/or progesterone and by the loss of the regulatory effects normally induced by interactions between these hormones.

In clinical practice, it has become increasingly apparent that depletion of all the ovarian hormones should be taken into consideration when hormone replacement is indicated for symptom control and/or disease prevention. Initial thinking that E alone would compensate for the hormones missing because of menopause led to the problem of endometrial hyperplasia and to increased risk of endometrial cancer in women with a uterus who were treated with unopposed E. It took about 30 years of experience with E replacement therapy before it was widely recognized that it was crucial to add a progestogen for women with a uterus.

It has also become apparent that E alone, particularly in women who have had a surgical menopause has often been inadequate for symptom control and disease prevention and that replacement of missing androgens is beneficial for these women. For women who are either surgically or naturally menopausal, understanding the dynamic relationships between Es, androgens and sex hormone-binding globulin (SHBG) and the clinical significance of these interactions can be essential to developing optimal hormone replacement.

Key concepts in developing an optimal hormone replacement program include: Es and androgens are produced every day during the reproductive phase of a woman's life; E depletion decreases SHBG production, whereas oral E replacement increases SHBG levels; oral methyltestosterone decreases SHBG production, whereas transdermal T appears to have little effect on SHBG levels (9); actions of androgens most often complement the actions of Es, and continuing decline in androgen production in the decade after menopause can lead to new medical issues in late postmenopausal women.

Menopause should be recognized as a biological turning point for the ovaries—from a reproductive to a postreproductive gland. The continuing function of the postreproductive ovary suggests a gland whose hormones serve to support functions that extend beyond reproduction and that are potentially significant for women throughout their lives.

CONSEQUENCES OF NATURAL MENOPAUSE

Ovarian hormones have hundreds of actions that support cell structure and function. Hormone depletion is associated

with altered function that may lead to symptoms, to pathophysiological effects, and eventually to disease processes. The consequences of menopause, whether natural or surgical, include symptoms that can affect a woman's capacity to function at home and in the workplace (10). The most common symptoms for which menopausal women seek professional help include vasomotor instability, sleep disturbance, and fatigue. These and other common signs and symptoms suggest reactions to hormone depletion in cell systems throughout the body, including the circulatory, muscle and skeletal, nervous, and urogenital systems. In addition to hot flushes and sleep disturbance, palpitations, angina-like chest pressure, headache, weakness, joint pain, decreased sexual desire, vaginal dryness, dyspareunia, anxiety, and depression have all been associated with menopausal hormone changes (11–13).

Menopause has also been related to the development of systemic diseases including urogenital atrophic conditions, atherosclerosis, osteoporosis, and dementia. Hormone replacement therapy (HRT) has proved efficacious for some of these conditions, whereas its effects on others, such as atherosclerosis and dementia, remain undetermined (14). The prevailing assumption in the development of HRT has been that the symptoms and disease processes affected by menopause are secondary to E depletion. As a result, E replacement therapy has become the standard of treatment with only passing recognition of the need to replace androgens.

There is reason to believe that androgen depletion may be a factor in menopause-related symptoms and disease processes formerly thought to be due entirely to E depletion. Women who have had a surgical menopause with removal of their ovaries have significantly lower levels of androgens than age-matched, naturally menopausal women and do show a difference in several regards. For example, the percentage of women reporting severe symptoms is significantly greater when menopause follows oophorectomy, an estimated 90% compared with the 50% of women experiencing a natural menopause (15). Other symptoms occurring with greater frequency and intensity in surgically menopausal women vs. naturally menopausal women include angina (16), migraine (17), urinary tract symptoms (15), sexual dysfunction (18), and depression (19). Women who have had a surgical menopause with oophorectomy often show inadequate symptom response to E-only treatment. Symptom control for these women is frequently only achieved with the addition of an androgen.

Androgen receptors are present throughout the body, and >200 cellular actions of androgens have been described. Significantly, surgically menopausal women show more than a twofold risk of myocardial infarction (16), stroke (20), osteoporosis (21), and clinical depression, (19) compared with the case of naturally menopausal women. In addition to showing improved symptom response when androgens are added to E replacement, postmenopausal women have also

shown better bone effects and better effects on sense of well-being and various dimensions of sexual function (18). An emerging area in cardiovascular research is a reassessment of the actions of androgens in arteries, with an ever-increasing number of studies showing protective, not detrimental, effects on cardiovascular function. These findings, taken almost entirely from male patients, are still of undetermined relevance for women's cardiovascular health.

Consideration of the clinical significance of androgens in postmenopausal women includes an understanding of the effects of E₂ depletion and E replacement therapy on bioavailable androgens as well as the significance of the ever-declining androgen levels during the postmenopausal years. Clinical studies indicate that androgens complement the actions of Es and also have independent actions that can affect function and prevent disease.

CLINICAL SIGNIFICANCE OF ESTROGEN DEPLETION EFFECTS ON SERUM FREE ANDROGENS

Estrogens stimulate SHBG production, and androgens suppress it. At menopause, E depletion and E replacement can have major effects on serum free androgen levels with clinically significant sequelae (22, 23). For example, increased levels of sexual desire have been observed in perimenopausal and postmenopausal women undergoing these hormonal changes. Masters and Johnson (24) report increased levels of sexual tension and sexual activity among some women in their late forties and early fifties. They cite psychological and sociocultural determinants, for example, "absolute contraceptive security" as the explanation.

Increased levels of sexual tension around the time of menopause have been problematic for some women and have been a reason for seeking help at the Yale Sex Counseling Service. Six of these women have been studied hormonally, and in each, the most significant finding appeared to be a low E₂ combined with an elevated free T. Because oral Es stimulate SHBG, treatment with oral Es has been our standard practice for these women. Reduction of sexual tension is reported within an average of 2 weeks, stabilizing at a comfortable level thereafter. Follow-up studies have indicated that the decrease in sexual tension correlated with a decrease in free T levels. All but one of the women whom we have treated over the years has responded to this approach. The one exception is important to recognize as she was later diagnosed to be acutely psychotic (Sarrel, PM, unpublished observations).

ACTIONS OF ANDROGENS IN POSTMENOPAUSAL WOMEN COMPLEMENT THE ACTIONS OF ESTROGENS

Symptom Control

As already mentioned, women without ovaries have more severe symptoms than do women who have had a natural

menopause, and androgen addition to E replacement is often necessary to bring these symptoms under control. The standard for treatment of hot flushes is E replacement. For example, Haas et al. (25) demonstrated the efficacy of transdermal E₂ in reducing the frequency and severity of hot flushes compared with placebo. However, in this as in most hot flush studies, there is a subgroup of women whose response remains inadequate, and they pose a challenge to the prescribing physician. Most often, doctors choose to increase the E doses, an approach that has not proved particularly effective.

The effectiveness of androgens in bringing hot flushes under control in women unresponsive to E-only treatment is described by Burger et al. (26). Seventeen postmenopausal women whose hot flushes and sweats were resistant to E-only treatment were studied. The women received an implant of E₂ and T and showed a significant response compared with the case of their prior treatment with E alone. Burger et al. (26) also reported significant improvement in concentration and energy level when these women received the E-androgen combination compared with when they were receiving E only. In a supportive study, Sherwin and Gelfand (18) compared treatment with E₂ alone and with treatment with E₂ and T and reported that the androgen had a significant effect on "sense of well-being." Among women visiting the Yale menopause program, fatigue has been one of the most common complaints. Frequently unresponsive to treatment with Es alone, as in the Australian studies of Burger et al. (26), fatigue in these women has responded positively to the addition of an androgen (Sarrel, PM, unpublished observations).

Disease Prevention

Prevention of osteoporosis is one of the main indications for HRT. Estrogens act as antiresorptive agents in bone and help maintain overall bone structure and function. Estrogen replacement therapies in general are indicated for osteoporosis prevention. However, it is well recognized that a significant proportion of women receiving Es continue to lose bone and that E alone is not adequate to protect these women (27). This is most often encountered in women who have had a surgical menopause, but it is not unusual in women who have experienced a natural menopause. Evidence that androgens inhibit bone resorption and stimulate osteoblast formation of new bone is seen in the studies of Raisz et al. (28). Serum markers of bone resorption and new bone formation were measured to demonstrate the differential effects of Es with and without the addition of methyltestosterone in postmenopausal women. The women receiving E showed a decrease in markers for new bone formation, whereas the women receiving E and androgen maintained their markers for bone formation, despite a reduction in bone resorption, suggesting an uncoupling of these processes. Watts et al. (29) treated postmenopausal women for 2 years, comparing the effects on bone density of esterified Es with and without

methyltestosterone. Changes in bone densities in the E-androgen-treated women were more than twice those of the E-only-treated women.

Another major area of concern in menopause medicine is the prevention of cardiovascular disease. Estrogen actions in arteries help prevent atherosclerosis and promote vasodilation, and there is considerable evidence for a cardioprotective effect of E replacement therapy (30). It is also known that the addition of potent progestins to HRT can oppose the protective effects of E and compromise the benefits seen with E alone (31). Because androgens have negative effects on lipid metabolism there has been concern that androgen addition to E treatment could also compromise the beneficial effects of Es. This does not appear to be the case; androgen actions in the arterial wall appear to support the vasodilator and antiatherosclerotic effects of Es (32, 33).

In a study of vaginal blood flow, Sarrel and Wiita (34) compared the effects of esterified Es with and without the addition of methyltestosterone and showed an enhancing effect of the methyltestosterone. In that study, the women had been previously treated with Es and had relatively elevated SHBG levels. When treated with the methyltestosterone, the SHBG levels declined and the free T levels were increased, changes that coincided with increased blood flow. More recent cardiology studies have demonstrated enhanced cardiovascular function in men with atherosclerotic disease who received intravenous and intracoronary T (35, 36).

ANDROGEN EFFECTS ON SEXUAL FUNCTION IN POSTMENOPAUSAL WOMEN

Changes in sexual function associated with menopause include decreased sexual desire, diminished sex response, dyspareunia, and decreased sexual activity (13). Biological, psychological, and sociocultural factors have all been described as related to these changes. From a biological viewpoint, the sexually significant effects of E depletion relate to decreased pelvic blood flow and sensory perception. Decreased pelvic blood flow in a hypoestrogenic state predisposes a woman to dyspareunia. Masters and Johnson (24) used the term *steroid starvation* to refer to these effects on sex response and reported restorative effects of HRT. Masters reported the use of Es and androgens for treatment of sexual complaints in menopausal women (37). Others pursued the effects of E alone. For example, Semmens and Wagner (38) studied vaginal blood flow in women treated with conjugated equine Es and showed an increase in flow that correlated with increased secretion and decreased dyspareunia.

In keeping with the predisposition to thinking of E deficiency as the most important biological determinant of menopausal sexual complaints, Sarrel (39) used a prospective, double-blind, E₂-placebo controlled approach to study various aspects of sexual function in healthy postmenopausal

women. A significant improvement in vulva blood flow and sensation, orgasmic response, vaginal cytology and secretion, and a marked decrease in dyspareunia was found during the 6-month treatment period. Sarrel (39) also reported an enhancement of sexual desire, loss of sexual desire being the most common sexual complaint at initiation of the study. Interestingly, when these women were treated with medroxyprogesterone acetate during the study, a decrease in genital blood flow, an increase in dyspareunia, and a loss of desire were recorded.

Others, however, did not confirm these findings except for the improvement, with E, in vaginal lubrication and decrease in dyspareunia. Sherwin and Gelfand (18) compared the sexual effects of E vs. E plus T in women after oophorectomy and found increased fantasy, desire, arousal, and frequency of coitus and orgasm in the women receiving both hormones. The earlier Burger et al. (26) study of enhancement of sexual parameters by T addition to E treatment has been more recently confirmed by Davis et al. (40). Women using Es but still complaining of loss of desire and reduced enjoyment of sex were treated with E₂-T implants and showed significant improvement. These women also showed a marked change in orgasmic capacity and initiation of sexual activity when they received the T.

Sarrel et al. (41) studied women who had been initially responsive to E-only treatment but who subsequently reported decreased sexual desire and diminished sexual responsiveness despite adequate E replacement. Using a prospective, blinded design to administer an esterified E vs. esterified E plus methyltestosterone protocol for an 8-week treatment period, the investigators reported enhanced desire and sensation when the women were receiving both hormones. The study included laser Doppler velocimetry to determine change in vaginal blood flow. The blood flow changes were significant with the androgen plus E compared with the levels after the placebo treatment period. Sarrel et al. (41) also studied the impact of the treatments on SHBG and free T levels and found that the levels did not change when the women stayed on the E-only treatment. When they received the E plus androgen, the women showed a significant decrease in SHBG and increase in free T levels. The investigators believed that the increased bioavailability of the steroids contributed to the enhancement of sexual function and desire and the increase in vaginal blood flow. Simon et al. (23) recently reported similar effects on SHBG and free T when comparing esterified Es with esterified Es combined with methyltestosterone.

In recent years prescribers of HRT have increasingly used a "continuous-combined" approach with women, using both an E and a progestin daily. Nathorst-Boos and Hammar (42) reported the effects of a continuous-combined regimen using an androgenic progestin, norethindrone acetate (NETA). They found statistically significant (all levels with $P < .001$) improvement in vaginal dryness, dyspareunia, sexual fre-

quency, and sexual problems as well as statistically significant ($P=.05$) levels of improvement in arousal and sexual enjoyment when the women used the NETA combined with E₂.

CONCLUSIONS

Natural menopause occurs at a time when androgen levels have decreased significantly from levels found during earlier decades in a woman's reproductive life. The major changes in hormone production at the time of natural menopause are the loss of E and progesterone. Androgens and Es most often act in concert with each other, and it appears that the loss of E at menopause serves to accentuate the relative depletion in androgens that occurs with aging. Menopausal E depletion decreases SHBG production, making more endogenous androgen available. As a result, endogenous androgens may prove sufficient for a while in controlling hormone deficiency symptoms and helping to prevent hormone deficiency-related disease. In some women, especially those who have had a surgical menopause but also including women who have had a natural menopause, E replacement does not appear to be sufficient to restore homeostasis, and optimal results are only achieved when androgens are added.

Ovarian hormones have widespread, significant effects on cell structure and function in almost every system of the body. Androgens are no exception to this. Therefore, when considering the postmenopausal impact of androgen deficiency, our thinking should not be limited to the effects on sexual function. We are only at the beginning of recognizing the importance of androgens in postmenopausal women.

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