ANDROGEN REPLACEMENT THERAPY IN POSTMENOPAUSAL WOMEN: CURRENT STATUS

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The benefits of conventional estrogen replacement therapy (ERT) with regards to reduction or elimination of vasomotor symptoms, prevention of urogenital atrophy, protection against osteoporosis, reduction of cardiovascular risk and improvement in cognition in postmenopausal (PM) women are generally well accepted. However there is still inadequacy of current ERT in the treatment of sexual symptoms in PM women. Sarrel *et al*. reported in a group of 252 naturally menopaused women that the incidences of vaginal dryness, dyspareunia and decreased libido were similar between women currently taking ERT and those who were not[1]. Androgens on the other hand are traditionally thought of as "male hormones". With the increase in the understanding of the role of androgens in normal female physiology, there is an increasing awareness of the sequelae of PM androgen deficiency.

Circulating androgens are secreted from the ovaries and adrenals in equal proportions in premenopausal women. The secretion of androgens from both sources declines with increasing age. At menopause, total estrogens secretion decreases abruptly by 80% whereas that of androgens only drops by 50% because the ovaries under the effect of luteinising hormone (LH) continue to produce testosterone at nearly normal levels. Surgical menopaused women on the other hand have an abrupt and more complete reduction in both estrogens and androgens production. Ovarian failure together with the age-related decline in adrenal androgens secretion constitutes the PM androgen deficiency state. This deficiency state is further aggravated if ERT is contemplated. Two mechanisms are responsible: (1) oral ERT will lead to an increase in sex-hormone binding globulin level which further reduces the free bioavailable testosterone level; (2) exogenous estrogens will suppress the LH stimulus to the PM ovaries. Although the mechanisms of androgen action in women are not well understood, this androgen deficiency state is believed to have resulted in a variety of physical and psychological symptoms that may affect the quality of life in PM women.

However, the therapeutic use of androgen replacement therapy (ART) in PM women is still controversial as only few long-term randomized studies have examined the benefits and risks of ART in PM women in detail.

The use of ART in PM women dated back as early as 1936 when MocQuot and Moricard reported its use to relieve vasomotor symptoms[2]. In the past 5 decades, almost all studies conducted had universally demonstrated a positive impact of ART on a number of parameters of sexuality in PM women over and above the effects achieved with ERT alone[3,4]. These parameters include libido, activity, satisfaction, pleasure, fantasy, orgasm and relevancy. The current consensus is that androgens should be considered in combination to ERT when there are inadequate responses to conventional ERT in the perspective of libido and sexuality.

In the perspective of psychological symptoms, there are few well-controlled studies and it is unclear whether ART effectively treats such symptoms in naturally menopaused women. However, in surgical menopaused women, combined androgen and estrogen replacement (CAERT) had been reported to result in greater improvement in appetite, well-being, energy level and a decrease in somatic and psychologic symptoms over ERT alone[5].

Concerning the role of androgens in the control of PM vasomotor symptoms, it was demonstrated that CARET provided the same improvement in vasomotor symptoms as did ERT alone[6]. Simon *et al*. in another study showed that the dose of estrogen could be halved but still achieved the same relief when androgen was combined with estrogen[7]. The current recommendation is that switching to CARET may provide addition relief to those PM women who do not achieve satisfactory relief for vasomotor symptoms with conventional ERT alone[8,9].

Another potential benefit of ART in PM women is in the area of osteoporosis. A number of observational studies have demonstrated a positive correlation between androgen level and bone density[10,11] and PM women with collapsed vertebrae were reported to have lower amount of bioavailable androgens than control[12]. Androgens have been demonstrated *in vitro* to have direct metabolic actions to stimulate bone formation, stimulate osteoblast differentiation and proliferation and inhibit osteoclast resorption though a proportion of its action is believed to be mediated through local aromatization to estrogens.

Watt *et al.* reported a significant increase of 3.4% in the vertebral bone density in 60 surgical menopaused women treated with CAERT for two years whereas the increase was insignificant for those treated with estrogen alone[6]. Young et al in a double-blind, randomized two-year study involving 291 surgical menopaused women reported a greater increase in lumbar and spine and hip bone mineral density in those treated with CAERT than in those treated with estrogen alone[13]. Biochemically, whereas ERT was able to decrease markers of bone resorption, CAERT also increased markers of bone formation after nine weeks of treatment in 28 PM women[14]. Despite all these evidences, the effect on incidence of fracture has never been addressed. In a primate model, the increase in bone density after ART was associated with an increase in intrinsic bone strength, increase in resistance to mechanical stress and an increase in torsional rigidity and bending stiffness of the tibia[15],

which theoretically should result in an increase in resistance to fracture.

Other potential benefits of ART include a favourable change in body composition and a suppression of both cell-mediated and humoral immune responses. Davis *et al*. demonstrated an increase in fat-free mass and a decrease in fat mass to fat-free mass ratio in PM women[3]. The effect on immunity was reported to cause symptomatic improvement in PM women with rheumatoid arthritis[16] though its role in autoimmune disorders needs to be defined with further studies.

Are there any risks associated with ART? Concerns have been casted on the issues of virilization and hirsutism, its negative effects on lipid profile and hence the cardiovascular risk, hepatotoxicity and its effect on breast cancer.

Previous reports on the issue of virilization and hirsutism were based on data obtained with outdated high dose androgen regimens. Current clinical evidence indicates that such changes are infrequent and mostly readily reversible with a reduction in dose. Based on an objective scale, Timmons *et al*. in a two-year randomized controlled study reported that there was no increase in incidence of hirsutism among those taking oral ERT alone or CAERT[17].

There are concerns that ART may nullify the beneficial effects of ERT on the lipid profile especially with reference to the adverse effect on high-density lipoprotein cholesterol (HDL-C). Clinical evidence has shown that the favourable effects of ERT on total cholesterol and low-density lipoprotein cholesterol are not diminished by either oral or parenteral androgen replacement. There is in fact an additional benefit of decreasing the triglyceride level with ART[6,18]. On the other hand, HDL-C level did decrease with ART when androgens were given orally but not parenterally[19]. However, the degree to which changes in lipid profile affect the long-term cardiovascular risk is unknown though epidemiological studies do not support androgen as a risk factor for cardiovascular diseases[20,21].

Although high dose of oral androgen therapy has potential toxic effects to the liver, hepatotoxicity has not been reported with physiological replacement doses in CAERT in which methyltestosterone is prescribed at a daily dose of 1.25 to 2.5 mg orally.

Concerning the effect of androgens on breast cancer, there is no conclusive evidence. High levels of androgens have been reported to be associated with carcinoma of the breast in both pre- and post-menopausal women[22,23]. But the presence of androgen receptors in breast tumours was associated with longer survival in operable cases and a favourable response to hormone treatment in advanced cases[24]. Neither is there any data on ART and recurrence of breast cancer.

In conclusion, the existing data suggest that CAERT can afford a variety of benefits to PM women namely a definite improvement in the domains of libido, sexuality and psychological well-being especially in those with surgical menopause, an additional relief for those with persistent or severe vasomotor symptoms, an improvement in bone density with a potential decrease in the risk of fracture, a favourable change in body composition and potential modulation of the immune system. The attendant risks of hirsutism, virilization and hepatotoxicity are minimal with modern low dose regimens. With the exception of a decrease in HDL-C levels with the oral route, beneficial effects on lipids are preserved especially if the parenteral route is employed. Effects on long-term cardiovascular risk and risk of breast cancers are unknown.

To sum up, the following recommendations on the indications for CAERT in PM women are suggested: (1) those ERT users with unsatisfactory sexual functions; (2) those ERT users who cannot achieve satisfactory relief for vasomotor symptoms; (3) those who have surgical menopause and (4) those ERT users who have or are at risk for osteoporosis. In some overseas centers notably the McGill University Menopause Clinic in Canada, it is a routine to give parenteral CAERT in the immediate postoperative period to women who have undergone surgical menopause with an aim to eliminate most of the symptoms associated with the abrupt onset of menopause unless they have endometrial cancer or other contraindications to hormone replacement therapy[25].

However, clinical guidelines for safe prescription of CAERT are still lacking. Whether it should be guided by symptoms or by serum testosterone levels is undefined. Davis in 1999 put forward the suggestion that the serum free testosterone levels should be restored to the upper end of the normal physiological range for young ovulating women to achieve a good therapeutic response[26]. There are ongoing researches on CAERT and its impact on female health is being pursued with research protocols that parallel those for conventional ERT in the fields of Alzheimer disease, cognitive function, breast cancer, lipid disorders and cardiovascular risk etc. It is anticipated that the role of CAERT probably will continue to expand with benefit provided to more PM women in the future.

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