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UNRESOLVED ISSUES IN ENDOMETRIAL CANCER AND POSTMENOPAUSAL HORMONE THERAPY

N S Weiss, S A A Beresford, L F Voigt, P K Green, J A Shapiro,
Fred Hutchinson Cancer Research Center, MP-381, 1124 Columbia St., Seattle, WA 98104, USA.

Despite several decades of epidemiologic research in this area, there are a number of questions pertaining to the relation of exogenous female hormones and endometrial cancer for which we do not have complete answers.

1.Among women who use unopposed estrogens, what happens to their risk of endometrial cancer once they stop? Does the risk ever return to that of women who have never used estrogens?

2.Are there some users of combined estrogen-progestogen hormone therapy in whom the incidence of endometrial cancer is increased (relative to that of hormone non-users), either on the basis of their monthly duration of progestogen or their total duration of combined hormone therapy?

3.Does the addition of a progestogen to postmenopausal estogen therapy lead to a reduction in the incidence of endometrial cancer of all stages and grades, or only the less severe forms of the disease?

These questions and others are being addressed in a population-based case control study of epithelial carcinoma of the endometrium in western Washington state (USA). Because of the large number of participants (832 cases and 1114 controls) and the relatively high frequency of hormone use in this population, this study will be able to provide relevant data bearing on each of the above issues.

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ANDROGENS DURING THE FEMALE LIFESPAN

H.M.Buckler and W.R.Robertson.
Dept. of Medicine & Endocrinology, Univ. of Manchester, Hope Hospital, Salford M6 8HD, UK

Androgens are precursors of oestrogens and the premenopausal ovary secretes them in higher quantities than oestrogens (<1000 pmol/l). Collectively the ovary and the adrenal contribute >10nmol/L of testosterone (T) and androstenedione (A). What then is the role of androgens in women?

Pre-pubertal girls have plasma T levels of <0.5nmol/L but these increase during puberty and together with the adrenal androgens (dihydroepiandrosterone; DHEA; dihydroepiandrosterone sulphate; DHEAS) control the growth of pubic and axillary hair. From 8-13 years DHEA and DHEAS increase around 20 fold to ~5μmol/L (the adrenarche) but are relatively stable through the menstrual cycle before falling with age due to decreased adrenal function.

Ovarian androgen secretion varies throughout the menstrual cycle being lowest (T ~ 1. 5nmol/L; A~7nmol/L) in the early follicular phase, rising to a peak at ovulation before falling during the luteal phase. As female sexual activity and libido also peak at mid-cycle androgens are likely to be associated with normal sexual function. The menopause is associated with a decrease in ovarian androgen secretion and following bilateral oophorectomy T and A levels fall by a further ~50%; these patients may have sexual dysfunction, tiredness and decreased feeling of well-being.

In view of the above there is a role for androgen and oestrogen treatment in post-menopausal women. The development of a new transdermal patch delivery system for T in women results in plasma levels in the desired therapeutic range with remarkably little within and between subject variability. As such they may be more satisfactory for use in women than existing preparations which are less physiological.

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ANDROGENS AND BONE FUNCTION

Susan Davis,
Director of the Slezak Research Program, The Jean Hailes Foundation, 291 Clayton Road, Clayton 3168, Victoria, Australia.

Androgrenic steroids appear to have an important physiologic role in the maintenance of bone mass in both men and women. Human osteoblastic cells possess androgen receptors, and androgens have been shown to directly stimulate bone cell proliferation and differentiation. Clinical research has demonstrated positive relationships between bone density and androgens in young, premenopausal and perimenopausal women and an association between declining androgen levels and bone loss in aging women. The antiresorptive effect of androgens on bone may be due to either a direct androgen action or mediated by oestrogens produced by local aromatization of androgen precursors. The role of androgens in maintaining skeletal integrity has been seriously questioned following the finding of severe osteoporosis in a male with normal testosterone levels and a defective oestrogen receptor. However, there is a body of evidence which supports a direct anabolic effect of testosterone on bone, independent of aromatization, and clinical data indicates testosterone replacement therapy may be useful in the prevention and treatment of osteoporosis in postmenopausal women. Positive correlations have also been observed between DHEA, DHEA-sulphate and bone mineral density in aging women and the effect of DHEA therapy on bone metabolism in postmenopausal women is currently being evaluated.

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THE USE OF ANDROGENS IN THE POSTMENOPAUSE - EVIDENCE FROM CLINICAL STUDIES

B B Sherwin,
Dept. of Psychology & Dept. of Ob/Gyn, McGill University, Montreal, P.Q., Canada, H3A 1B1

During the past decade, numerous prospective, controlled studies have documented the clinical efficacy of adding androgen to an estrogen replacement regimen for the treatment of postmenopausal women. Combined estrogen-androgen therapy increases well-being and energy level over and above treatment with estrogen alone. Second, although estrogen is critical for the integrity of female reproductive tissues, testosterone is important for the maintenance of sexual desire and interest in women, just as it is in men. Studies on non-human primates suggest that testosterone exerts this effect on sexual desire by acting directly on the brain rather than on peripheral tissues. Women who respond best to combined treatment are those in whom the decrease in sexual desire occurred coincident with the hormonal changes at menopause. Small amounts of exogenous testosterone also increase bone mass in postmenopausal women. Possible adverse effects of estrogen-androgen combined replacement include facial hirsutism which is dose-dependent. When administered intramuscularly, combined treatment does not induce a more atherogenic lipoprotein lipid profile. However, there is some evidence that combined oral preparations may lower HDL cholesterol while also reducing total and LDL cholesterol compared to estrogen alone.