Each tissue becomes master of its sex steroid environment at menopause

I truly appreciated your recent Editorial entitled ‘Menopause – natural selection or modern disease?’1. It seems reasonable to believe that menopause is part of natural selection, possibly by allowing women to help raising the grandchildren2. Stopping having children at 50 years seems a positive result of evolution for a better quality of the human species.

Menopause should also be considered a modern disease resulting from the important number of years recently added to the life span due to the success of modern sanitary and medical discoveries. In fact, women now live 40% of their lives in postmenopause with a progressive deficiency in sex steroids, a problem practically absent 75 years ago when duration of life was of the order of 50 years. It is thus very important, as you indicate, to strive at making our aging population as healthy as possible and to develop the ideal ‘hormonal’ therapy, with only benefits and no risks which could therefore be presented almost universally3. Menopause is thus both the result of natural selection4 and a modern disease and not only natural selection or only modern disease.

Menopause is well recognized to be linked to the cessation of estrogen secretion by the ovaries, thus avoiding stimulation of the endometrium potentially leading to cancer, a problem associated with estrogen-based hormonal replacement therapy5. It must be remembered that the serum levels of estradiol, the main estrogen in women, must always remain at biologically inactive concentrations or below 9.3 pg/ml, the 95th centile of serum estradiol concentrations measured by validated liquid chromatography/tandem mass spectrometry, the only method providing accurate and reliable values4. Women, however, still need a physiological intracellular supply of estrogens and androgens for the normal functioning of most, if not all tissues, except the endometrium which should not be stimulated by estradiol. Since the exclusive source of sex steroids after menopause is DHEA (dehydroepiandrosterone), mostly of adrenal origin5, the difference between symptomatic and asymptomatic women is not related to estrogens but must be exclusively associated with differences in the availability of DHEA between women. In fact, all postmenopausal women are in the same situation regarding estrogens, with no biological estrogen secretion in the circulation, thus protecting the uterus and probably other tissues6. Consequently, all the differences in sex steroid availability between women must be related to differences in DHEA availability.

This new understanding of sex steroid physiology in women follows the cloning and characterization of the long series of steroidogenic enzymes in the peripheral tissues, which transform the inactive precursor molecule DHEA into specific intracellular concentrations of estradiol and testosterone, according to the local needs and the expression of the required enzymes in each tissue7. In agreement with the mechanisms of intracrinology, the active sex steroids made intracellularly at their sites of action are also inactivated locally in each cell/tissue before being released as inactive metabolites in the circulation, from which they are excreted by the liver and kidney8.

With an approach based upon the normal physiology of sex steroids in women, one could possibly hope to be able to prevent the problems of menopause, as suggested1, instead of waiting for the many years spent in a sex steroid-deficient environment to cause a serious deterioration of health. While the aging process is an unavoidable reality, it appears reasonable to attempt to correct and possibly even prevent the deterioration of health in women by correcting the sex steroid deficiency, which is exclusively related to low DHEA activity after menopause2,5. The recent data obtained in large-scale, placebo-controlled clinical trials, showing the beneficial effects of intravaginal DHEA on the symptoms and signs of vulvovaginal atrophy performed according to the guidelines of the US FDA, can be seen as a significant progress in the direction of a ‘physiological’ response to the sex steroid deficiency of menopause5–7. Moreover, may it be that physiological treatments could lead to clinically acceptable prevention of the ‘increasingly problematic’ problems of menopause which accompany the ever-increasing duration of life7.

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References

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