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MHT: past mistakes, future directions

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The adverse outcomes seen in The Women's Health Initiative (WHI) combined hormone therapy trial were mainly to an over-dosage of menopause hormone therapy (MHT) in a relatively elderly population. However, fundemental differences exist between conjugated equine estrogens and 17 beta estradiol and between medroxyprogesterone acetate and other progestogens. It is likely that these differences also contributed to the adverse outcomes in WHI, which were contrary to the cardiovascular benefits seen in previous observational trials.

In addition to binding to the progesterone receptor, many progestogenic compounds also bind to the glucocorticoid, mineralocorticoid and androgen receptors. This can lead to unwanted effects such as unfavourable glucose metabolism, fluid retention, acne, weight gain. Recent studies of cardiovascular risk markers in younger women have therefore been designed using predominantly 17 beta estradiol and progesterone or dydrogesterone as primary interventions.

Menopause societies are now advising that natural progesterone and dydrogesterone may have more favourable metabolic and breast effects compared to synthetic progestogens. Natural progesterone and dydrogesterone do not attenuate the beneficial effects of estradiol in reducing insulin resistance and arterial compliance. There also appear to be differential effects of progesterone and progestogens on breast tissue. Progesterone has a neutral and dydrogesterone a pro apoptotic effect on breast epithelial cells, whereas androgenic progestogens such as medroxyprogesterone acetate appear to have a proliferative effect, possibly through non specific effects on glucocorticoid receptors and gene expression. This might explain the small increase risk in breast cancer promotion in some studies when synthetic progestogens are combined with estrogen. Observational data such as the French E3N cohort and the Finnish registry cohort suggest that women using natural progesterone and dydrogesterone are not at increased risk of breast cancer within the first 5 years of use; these data should be confirmed by long term, randomised prospective studies.

Thus, replication of the physiological hormonal environment with estradiol and favourable types of progestogens and progesterone can maximise benefits and minimise side effects and risks of MHT. It is time we moved away from the notion, often propagated by epidemiologists and the media, that all hormone therapy products have a single class effect.

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