Long-Term Use of Contraceptive Depot Medroxyprogesterone Acetate in Young Women Impairs Arterial Endothelial Function Assessed by Cardiovascular Magnetic Resonance

To the Editor:

In their interesting study, Sorensen et al. demonstrated in young women that contraceptive depot medroxyprogesterone acetate (MPA)-induced hypoestrogenism may impair endothelium-dependent arterial function as measured by cardiovascular magnetic resonance. According to Hashimoto et al., endothelium-dependent vasodilation varies during the menstrual cycle, and endogenous estradiol may be involved in this menstrual cycle-related vascular function. In addition, endothelium-dependent vasodilation decreased in women with low plasma concentrations of estrogen, whereas estrogen replacement improved endothelial function by increasing expression of endothelial nitric oxide synthase. Thus, endothelium-dependent vasodilation may be regulated in part by ovarian hormones such as estrogen.

Our previous findings also demonstrated that concurrent administration of clinical doses of MPA offsets favorable effects of estrogen on endothelial function in postmenopausal women. However, plasma levels of estrone and estradiol did not differ between estrogen alone and estrogen plus MPA groups, indicating that additional factors may affect endothelial function.

Because testosterone derivatives can exert vasoconstrictor influences, androgenic properties of MPA may be responsible for the endothelial dysfunction. MPA has been reported to have an androgenic effect by activating androgen receptor-regulated pathways. In contrast, the addition of micronized progesterone, which has less androgenic effect than MPA, does not attenuate those favorable effects of estrogen. Thus, the impact of MPA on endothelial function may be related to its androgenic potency as well as hypoestrogenism.

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Response

Dr. Wakatsuki and colleagues suggest that endothelial dysfunction with long-term use of depot medroxyprogesterone acetate (DMPA) is partly explained by the androgenicity of the progestogen. The link between detrimental cardiovascular effects and the androgenicity of progestogens is being put forward frequently to explain why certain progestogens prescribed with estrogen in hormone replacement therapy (HRT) counteract the effects of estrogens on cholesterol metabolism and the vascular. However, to view only the vascular effects of progestogens based on their affinity for the androgen receptor is simplistic, as progestogens are complex hormones and their cardiovascular effects are diverse. Not only is the progesterone receptor itself expressed in vascular tissues, but progestogens also have variable cross-affinity for other steroidal receptors (eg, the mineralocorticoid receptor), which might also cause cardiovascular effects.

In addition, the effects of androgens in the female circulation are far from understood, and data are emerging favoring a broadened view. For instance, aromatase conversion of androgens to estrogens has been directly linked to inhibition of atheroma development.1

Our data indicate that estrogen suppression is probably the major reason for endothelial dysfunction with long-term DMPA use, with a possible synergistic effect of high-density lipoprotein lowering.2 Our study does not concur with any direct negative vascular effect of MPA, as we did not measure any additional detrimental endothelial effects during peaking serum levels of MPA; this is particularly noteworthy as the MPA dosages we assessed were at least 30 times the dosages normally prescribed in HRT preparations. However, the mechanism suggested by Dr. Wakatsuki and colleagues needs further study. We also believe that the study of the cardiovascular effects of progestogens and androgens are of considerable scientific importance.

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