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

To the Editor:

Published epidemiological and biological data regarding the injectable contraceptive depot medroxyprogesterone acetate (DMPA) do not support the authors’ contention that use of this important birth control method adversely impacts cardiovascular health. On the basis of their comparison of peripheral arterial hyperemia-induced flow-mediated dilatation (FMD) between women using DMPA and nonusers, Sørensen and colleagues conclude that DMPA might adversely affect cardiovascular health. Specifically, FMD was reduced in DMPA users, but not in untreated ovulatory women.

Although the authors appropriately did point to the World Health Organization (WHO) Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception, which did not demonstrate an elevated risk of cardiovascular events with use of DMPA, they failed to note that other reports from this same study have demonstrated that use of combination oral contraceptives (OC) overall elevates the risk of venous thromboembolism and, in women who smoke, increases risk of myocardial infarction as well as stroke.

In contrast to combination OC (which contain estrogen and progestin), use of the progestin-only DMPA does not appear to increase hepatic production of coagulation factors or increase blood pressure. The absence of these changes have led the American College of Obstetricians and Gynecologists to suggest use of DMPA in women for whom use of combination OC is considered unsafe. Such women include smokers over age 35; those with a history of thromboembolism; and women with coronary artery disease, cerebrovascular disease, congestive heart failure, diabetes with vascular disease, or severe hypertriglyceridemia.

The clinical implications, if any, of reduced FMD in healthy young women are unknown. Recently, conjugated estrogen combined with medroxyprogesterone acetate was reported to increase FMD of the brachial artery in menopausal women. Although many speculated that such apparent improvements in arterial function meant that menopausal hormonal replacement would prevent coronary artery disease, the findings of the Women’s Health Initiative have taught us otherwise and have also reminded us of the importance of relying on direct outcomes (eg, cardiovascular events) rather than indirect, surrogate markers such as vascular reactivity when making clinical decisions.

Globally, millions of women rely on DMPA for birth control. Given the reassuring epidemiological safety data surrounding DMPA use and favorable observations regarding coagulation factors and blood pressure, along with the unknown clinical implications of FMD changes in young healthy women, the authors’ data do not justify their conclusion that use of this highly effective, convenient injectable contraceptive might adversely impact cardiovascular health.

Disclaimer

Dr Kaunitz’s Department (University of Florida) receives clinical trial support from Pharmacia (manufacturer of DMPA) and Johnson and Johnson (manufacturer of OC). In addition, Dr Kaunitz serves as a consultant and speaks for Pharmacia and Johnson and Johnson.

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Response

We thank Professor Andrew Kaunitz for his interest in our article recently published in Circulation regarding reduced endothelial function and hypoestrogenemia in long-term users of depot medroxyprogesterone acetate (DMPA).

Although we acknowledge the relative safety of DMPA and its very important role as an excellent contraceptive with definite physiological response has been shown to possess direct predictive potential for future cardiac morbidity. Estrogens directly enhance endothelium-dependent arterial reactivity in pre- and postmenopausal women. Combination with MPA has been shown to inhibit this endothelial response in postmenopausal women, however, which might partly explain why the combination of conjugated equine estrogens and MPA was not found to reduce postmenopausal cardiac morbidity. Interestingly, these findings directly contradicted numerous case-control studies, which emphasizes the fact that the latter type of data cannot stand alone to establish causality or safety.

Our findings indicate potential adverse CVD risk associated with hypoestrogenism in long-term users of DMPA and encour-


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