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\(^1\) 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.\(^2\)

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 has 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.\(^3\)

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.\(^4\) 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\(^5\) have taught us otherwise and 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.\(^2\)

We thank Professor Andrew Kaunitz for his interest in our article\(^1\) recently published in *Circulation* regarding reduced endogenous 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 advantages, it is now recognized by major authorities such as the World Health Organization (WHO) and the International Planned Parenthood Association that long-term use of DMPA is associated with hypoestrogenism.\(^2,3\) Additionally, most experts concur that menopausal oestrogen deprivation is associated with potential arterial health risk, as is the case with premature ovarian failure. On the basis of the available evidence, which is now supported by the data we put forward, it is not possible to reassure long-term DMPA users that their oestrogen deprivation is without detrimental vascular effects.

The WHO study mentioned in our publication and also by Professor Kaunitz is hampered by the fact that arterial disease is rare in the young populations studied. It contained few DMPA users, was confounded by the fact that DMPA users may have used add-back estrogen to deal with irregular bleeding, and did not address long-term impacts of use. The study did indicate that DMPA use is linked to some cardiovascular disease (CVD) risk in women with hypertension. There was sufficient concern for the WHO to state in its eligibility criteria for contraceptive use that DMPA is “not usually recommended” in women with multiple CVD risk factors (including older age and smoking) and in women with hypertension.\(^2\)

Our study demonstrates a potential adverse effect of DMPA that requires further large-scale study. We used a validated technique for measurement of endothelial function, which as a physiological response has been shown to possess direct predictive potential for future cardiac morbidity.\(^4\) 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,\(^2\) 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-
age the conduct of larger-scale longitudinal studies with assessment of clinical outcome. Notwithstanding the important clinical role of DMPA, the burden of proof is on those who deny any possibility of an adverse effect to demonstrate this scientifically.

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