Estrogens, Progestins, and Atherosclerosis

To the Editor:

We feel compelled to comment on the Brief Review “Should progestins be blamed for the failure of hormone replacement therapy to reduce cardiovascular events in randomized controlled trials?” by Koh and Sakuma.1 Specifically, although we agree with the suggestion that the effects of estrogen on the vasculature may depend on the extent and severity of existing atherosclerosis, we disagree with the assertion that “added progestin does not negate the beneficial effects of estrogen” and the implication that all progestins affect the vasculature equivalently. Our objections are based on the authors’ incomplete and misleading summary of the animal studies relating to estrogen and progestin effects on atherosclerosis and vascular responsivity.

Koh and Sakuma’s misstatement in this regard is important, because most clinical and epidemiological data on the subject come from studies of populations of older postmenopausal women or those with preexisting atherosclerosis. Evidence is accumulating that hormone replacement therapy may not have cardiovascular benefit in these populations. However, effects on younger women or those with little preexisting atherosclerosis are still unclear and a matter of controversy. Animal studies provide the largest body of data addressing the effects of hormone replacement on atherosclerosis extent and vascular responsivity in individuals with little or no preexisting disease.

The authors state correctly at the beginning of their section Experimental and Animal Studies that “synthetic, not natural progestins, interfered with estrogen protection against vasoconstriction” and cite the studies of Miyagawa et al. and Miller et al. However, they neglect to mention the 2 additional studies of Williams et al. demonstrating antagonistic effects of medroxyprogesterone acetate (MPA) on conjugated equine estrogen (CEE)-induced promotion of endothelium-dependent dilation in atherosclerotic monkeys. The authors also fail to cite a third study of Williams et al. showing the lack of an antagonistic effect of the progestin nomegestrol acetate. Together, these studies contradict the authors’ contention that progestin does not negate beneficial effects of estrogen. Rather, the data strongly suggest that some progestins, particularly MPA, antagonize the protective effects of estrogen against endothelium-mediated vasoconstriction.

Next, the authors correctly note that cyclic progestrone does not antagonize the effects of estradiol on arterial low-density lipoprotein accumulation in monkeys but fail to note a similar lack of an effect of cyclic progestrone on estrogen-mediated inhibition of atherosclerosis in monkeys. Furthermore, they fail to cite the studies of Hanke et al. Among these, but not all, doses of continuously administered natural progesterone antagonized inhibitory effect of estradiol on atherosclerosis in ovariectomized rabbits.

Finally, when assessing the 2 largest monkey studies bearing on this issue, one reporting that MPA diminishes the atheroprotective effects of estrogen and the other finding that MPA does not, the authors inexplicably choose to emphasize the latter finding by stating that “this study confirms that MPA did not attenuate the effects of CEE to reduce atherosclerosis.” In fact, there are reasons to think that the results of the former study are more clinically relevant than the outcome described in the latter. First, in the Adams study the monkey equivalent of 2.5 mg MPA was administered once a day, as it is to postmenopausal women, whereas in the Clarkson study the same amount was administered in divided doses twice a day. As a result, the endometrial histology in the 2 studies was strikingly different. In the Adams study, endometrial hyperplasia induced by CEE was completely antagonized by MPA (as would be expected in postmenopausal women using MPA), whereas in the Clarkson study it was only partially antagonized. It seems possible that, because twice daily administration of MPA failed to produce the expected and desired endometrial effect, it would also fail to produce the effect on the artery predicted by the Adams study.

In summary, although in some cases progestins do not appear to antagonize favorable effects of estrogen, it is also clear that in many other cases they do. A complete and unbiased review of existing data does not support the conclusion that “added progestin does not negate the beneficial effect of estrogen” or that all progestins behave similarly. Therefore, it remains possible that some, but not all, forms of hormone replacement therapy might have favorable cardiovascular effects in younger peri- or postmenopausal women without preexisting advanced atherosclerosis. We believe that this remains an important issue that requires further study.

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Adams et al claim we asserted in our review that added progestin does not negate the beneficial effects of estrogen and that all progestins affect the vasculature equivalently. They also blamed us for an incomplete citation of the animal studies; however, this is not true. In our review, we quoted and presented both positive and negative studies. Indeed, there have been more than a few studies showing controversial results regarding the effects on vasomotion in both animal and clinical studies. We summarized these controversial results and concluded inconsistency in the effect of vasomotion. However, we could not cover all published animal studies because this particular issue was not a unique scope of our review.

We agree with their hypothesis that some forms of hormone replacement therapy might have favorable cardiovascular effects in younger peri- or postmenopausal women without preexisting advanced atherosclerosis. This conclusion is one of the purposes of our review. We proposed the importance of the stage of atherosclerosis at the time of initiation of hormone or estrogen replacement therapy.

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