A Mouse Model of the Perimenopausal Transition
Importance for Cardiovascular Research

J. Koudy Williams

The postmenopausal population of the U.S. is expected to reach 40 million in the next decade, accounting for ~33% of all women and 15% to 20% of all adult Americans. Cardiovascular disease (CVD) will be a leading cause of death among these women, while osteoporosis and resulting fractures will affect up to half of women, and many others will experience significant cognitive decline. Results of prospective clinical trials indicate that neither estrogen nor estrogen + progestin hormone therapy reduces the risk of CVD in postmenopausal women.\(^6\)\(^-\)\(^9\) As such, a major interest of health professionals is to better understand the determinants of CVD risk of women before becoming postmenopausal.

The risk of CVD in women increases with age.\(^4\)\(^,\)\(^5\) During the years leading up to the menopause (the perimenopausal transition), women experience reductions in sex hormone production (estrogens and androgens) that also may be associated with subsequent CVD risk.\(^6\)\(^-\)\(^9\) However, the extent to which postmenopausal CVD risk is age-associated, influenced by perimenopausal changes in hormone production, or both, cannot be disentangled using animal models that rely on oophorectomy. Studies by Matthews et al 1994 and 2001 provide several lines of evidence that cardiovascular risk begins in the perimenopause.\(^5\)\(^,\)\(^7\) CVD risk factors, such as declining plasma HDLC concentrations and increasing plasma LDLC concentrations, begin in the perimenopause. Additionally, increased pulse pressure (an index of arterial stiffness) increases early in the perimenopause and is associated with increased intimal/medial thickness of the carotid artery in the menopause.\(^7\) It is also reported that impaired nitric oxide–mediated vasodilation, which precedes the development of atherosclerosis and is predictive of future coronary events in humans,\(^10\)\(^,\)\(^11\) changes over the menstrual cycle of women\(^12\)\(^-\)\(^14\) and that reduced dilatory capacity of arteries is directly associated with the low plasma estradiol concentrations. Thus, even short-duration estrogen deficiency (as occurs during the menstrual cycle) appears to increase the risk of CVD. It then stands to reason that more pronounced and long-term estrogen deficiency, as occurs during the perimenopausal transition, might initiate changes in arterial pathophysiology that precludes increased CVD risk.

The unique ability of this mouse model of 4-vinylcyclohexene diepoxide (VCD)-induced perimenopause-associated ovarian senescence can be used as: (1) a more reproductive–physiologically relevant animal model of the perimenopause and the postmenopause; (2) a model in which to test the independent, additive, or interactive effects of age and sex hormone changes on CVD risk; and (3) an animal model which facilitates the examination of gene expression on the pathogenesis of CVD risk during these life stages of women.

In this issue of *Arteriosclerosis, Thrombosis, and Vascular Biology*, Mayer et al report that estrogen inhibits atherosclerosis across the VCD-induced perimenopausal transition.\(^15\) This is an important first step in defining better the effects of exogenously administered sex hormones on cardiovascular risk. This model will also be useful in dissecting out the effects of several perimenopausal-associated pituitary-ovarian hormone changes (eg, follicle-stimulating hormone [FSH], androgens) on cardiovascular end points. Although the present study examined the effects of perimenopausal estrogen administration on atherosclerosis extent, other end points (vascular reactivity, plaque inflammation, response to artery injury, thrombosis, myocardial ischemia) could also be evaluated using this model.

With the use of any drug-induced physiological changes, care will need to be taken to assure that the drug has no direct effects on the tissue in question. Therefore, with each new end point, a companion (or preliminary) study will need to be completed in oophorectomized mice to assure no direct effects on the end point in question. Nonetheless, this novel animal model has great potential in identifying and studying changes in vascular pathobiology occurring during the perimenopausal transition.

Women with perimenopausal symptoms (hot flashes, mood changes) and those at increased risk of osteoporosis will continue to inquire about hormone therapy during their peri- and postmenopausal years. It behooves health professionals and researchers to provide the most learned information about the benefits and risks of hormone therapy throughout the complete life cycles of women. This model could greatly help provide preliminary data concerning the health benefit/risk profile during the understudied perimenopausal transition.

**References**


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