Gynecological Endocrinology

ISSN: 0951-3590 (Print) 1473-0766 (Online) Journal homepage: informahealthcare.com/journals/igye20

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Michael Mendelsohn

To cite this article: Michael Mendelsohn (2008) Hormones and cardiovascular disease, Gynecological Endocrinology, 24:9, 483-484, DOI: 10.1080/09513590802296138

To link to this article: https://doi.org/10.1080/09513590802296138

Published online: 07 Jul 2009.

Gynecological Endocrinology, September 2008; 24(9): 483–484

informa
healthcare

EDITORIAL

Hormones and cardiovascular disease

MICHAEL MENDELSOHN

Elisa Kent Mendelsohn Professor of Molecular Cardiology and Medicine Tufts University School of Medicine Chief Scientific Officer Director, Molecular Cardiology Research Institute Tufts Medical Center

The effect of hormone replacement therapy (HRT) on heart disease has been a controversial topic in recent years, due especially to the confusing and often heated discussions about the results of the Women's Health Initiative (WHI) study. However, the pendulum has now swung back toward the viewpoint that HRT in menopausal women is beneficial for cardiovascular health, which many gynecologists have advocated all along. Recent clinical data are quite consistent with the two decades of extensive basic and animal research on the vascular biology of estrogen [1,2] and with the many observational studies of HRT [3] in supporting that estrogen has beneficial effects on blood vessels.

The WHI estrogen plus progesterone study reported that HRT increased cardiovascular events, raising concerns about the overall safety of HRT [4], while the estrogen-only arm of the WHI study (WHI-CEE) demonstrated no increase in cardiovascular events and suggested a potential benefit of conjugated equine estrogens (CEE) on heart disease in 50–59-year-old women. However the WHI-CEE arm was stopped prematurely, before a definitive answer could be provided regarding this issue [5,6]. Recent WHI analyses have better addressed the question of a beneficial role for HRT in cardiovascular disease (CVD) and support the 'timing hypothesis' for HRT, which states that the beneficial effects of HRT in preventing atherosclerosis occur only when HRT is initiated before advanced atherosclerosis has developed [2,7,8].

A recent WHI analysis focused specifically on the importance of HRT timing and showed that women in WHI who initiated HRT during their fifties or within 10 years of menopause tended to have a reduction in coronary heart disease (CHD) events compared with women more distant from menopause [9]. The timing hypothesis predicts that HRT loses its beneficial effects when given to older women because the underlying biology of the vessel wall and the vascular response to HRT are altered in older, more atherosclerotic vessels. This hypothesis arose from the seminal studies of Clarkson and colleagues in primates [8], as well as others [2,7].

Last summer, Manson and associates reported the results of the WHI-Coronary Artery Calcium Study (WHI-CACS), an ancillary study of a younger subset of the original WHI-CEE cohort, examining the effects of CEE on coronary artery calcification [10] which is a marker for the extent of underlying atherosclerosis and the risk of future cardiovascular events [11]. The results of the WHI-CACS were clear: women assigned to CEE had significantly less coronary arterial calcification than women assigned to placebo. WHI-CACS enrolled 1064 women who were on average 55 years old, 12 years past surgical menopause and treated for 7.4 years. Intention-to-treat analyses showed that CEE reduced coronary calcification by 42% ($p = 0.03$) and this reduction was even more dramatic in women adherent to their estrogen (61%; $p = 0.004$), an outcome unaffected by multi-variable adjustment.

Estrogen has multiple, complex effects on the blood vessel that are mediated by the same estrogen receptors that mediate hormonal effects in reproductive tissues [1,2,7]. Estrogen receptors are required for normal vascular physiology and for estrogen-mediated protection against vascular injury and atherosclerosis [12,13]. Estrogen receptors may be expressed at different levels in blood vessels as atherosclerosis progresses and/or estrogen regulation of specific gene targets may be different in young vs. old vessels. The WHI was designed to prospectively examine the effects of HRT on CHD in women. However, since CHD events in younger women are uncommon, WHI enrolled predominantly older women. In retrospect,

Correspondence: M. Mendelsohn, Tufts Medical Center 750 Washington Street, Box #80 Boston, MA 02111. Tel: (617) 636-9370. Fax: (617) 636-1444. E-mail: mmendelsohn@tuftsmedicalcenter.org

ISSN 0951-3590 print/ISSN 1473-0766 online
DOI: 10.1080/09513590802296138

the lack of CHD benefit in the WHI is not surprising: the results were driven mainly by effects in older women who in clinical practice are rarely considered for HRT. Unfortunately, the initial WHI results were over-extrapolated, creating widespread concern that HRT is neutral or even harmful for CVD for all women, including younger women considering HRT for relief of menopausal symptoms.

It remains important to emphasize that HRT is not a primary preventive strategy for CVD in women, for which there are proven effective therapies that remain underutilized. However, recent consensus statements from our two largest societies of menopausal practitioners [14,15] strongly endorse the timing hypothesis and recognize the potential beneficial cardiovascular effects of HRT in younger menopausal women receiving therapy for symptoms. The pendulum has truly swung back to a position more consistent with the large body of experimental data supporting the beneficial effects of estrogen on the blood vessel wall.

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