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Reproductive Health as a Marker of Subsequent Cardiovascular Disease:

The Role of Estrogen

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Cardiovascular disease (CVD) kills 1 in 3 women worldwide,[1] and the risk of CVD increases markedly after the cessation of ovarian function at menopause.[2] Although the dramatic decline in estrogen levels following menopause has been implicated in the loss of cardioprotection in women, the association between the decline in ovarian function and vascular disease may be even more complex.[2] The menopausal transition is associated with significant changes in the vascular system, distribution of body fat, blood pressure, and blood lipid levels,[3] all of which increase the risk of CVD. However, the possibility of shared risk factors, including genetic, lifestyle, and environmental, for both early menopause and elevated CVD risk warrants consideration. Key questions are whether early cessation of reproductive function etiologically increases risk of CVD or whether latent cardiovascular disease causes reproductive aging and accelerates the onset of menopause (or both).

Menopause occurs at an average age of 51 years in Western populations, but the range of age at onset is wide, with most women experiencing menopause between ages 40 and 60 years.[3,4] Approximately 10% of women experience menopause younger than 45 years and consequently have a shorter total duration of premenopausal estrogen exposure than women with later-onset menopause. As shown in the meta-analysis in this issue of *JAMA Cardiology* by Muka et al,[5] women with early menopause have an increased risk of overall coronary heart disease, fatal coronary heart disease, CVD mortality, and all-cause mortality. However, most studies are unable to assess directionality of the association between early natural menopause and CVD risk. The potential for pre- or perimenopausal cardiovascular risk factor status to predict early menopause was addressed in the Framingham Heart Study,[6] which found that increases in cholesterol, systolic and diastolic blood pressures, and other vascular risk factors prior to menopause were each associated with future menopause at a significantly younger age, even after adjusting for smoking. Such data provide intriguing support for the hypothesis that cardiovascular health may contribute to the timing of

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menopause but do not preclude a bidirectional association. Shared risk factors, such as smoking, which has been associated with both early menopause and increased CVD risk, other risk factors, and shared gene variants for both outcomes may also be contributory.[3,4]

An additional line of evidence for an adverse effect of early loss of ovarian hormones on vascular outcomes derives from research on women with early surgical menopause and bilateral oophorectomy. Oophorectomy before menopause leads to an abrupt reduction in endogenous estrogen and androgen production.[3,4] In a meta-analysis of observational studies,[7] early bilateral oophorectomy was associated with more than double the risk of CVD (relative risk, 2.62; 95% CI, 2.05–3.35). Moreover, several studies have indicated that women who have early oophorectomy followed by treatment with exogenous estrogen therapy do not experience heightened risks of coronary or CVD events compared with women with intact ovaries.[3]

What is the role of menopausal hormone therapy (HT) for women with early natural menopause? Importantly, women and clinicians should understand that the results of the Women's Health Initiative, which enrolled postmenopausal women aged 50 to 79 years (mean age, 63 years), should not simply be extrapolated to women experiencing menopause younger than 45 years. Professional societies agree that women with early menopause (natural or surgical) and without contraindications for HT use should be considered for hormonal replacement until at least the average age of menopause for the purpose of preserving bone and vascular health as well as for symptom management.[3,4] Women who underwent hysterectomy can be treated with estrogen alone, while women with an intact uterus require both estrogen and a progestogen. Although the distinction between early menopause and menopause at an average age is crucial for clinical decision making about HT, it is important to emphasize that recent detailed analyses from the Women's Health Initiative indicate that absolute risks of adverse events related to HT were much lower for younger women aged 50 to 59 years than for older women.[8] Moreover, in the estrogen-alone trial, women aged 50 to 59 years had more favorable results for all-cause mortality, myocardial infarction, and the global index than did older women, and in the estrogen plus progestin trial, an elevated risk of myocardial infarction with HT was present only in women more than a decade past menopause onset.[8] The Early vs Late Intervention Trial with Estradiol[9] also provided evidence for the timing hypothesis, with favorable effects of estradiol on slowing atherosclerosis progression among women in early, but not later, menopause. Thus, recent evidence also provides reassurance about the use of HT for symptom management among women in their 50s, but HT is not recommended for the express purpose of preventing CVD or other chronic diseases in women with an average age at menopause onset.[3,4]

Finally, gonadal dysfunction and cardiac toxicity are associated with cancer treatments, and cardiovascular disease is the leading noncancer cause of late mortality among survivors of childhood and adolescent cancer. In a recent cross-sectional cohort study of survivor outcomes, 7.4% of males and females had cardiomyopathy and 3.8% had coronary artery disease.[10] These risks are associated with anthracyclin drugs, specifically doxorubicin, and radiation therapy to the pleural region. As gonadal damage can also occur from these

treatments, dissecting the contribution of endocrine dysfunction to disease progression is an important challenge for future research relevant to this patient population.

In conclusion, early menopause serves as a sentinel for elevated CVD risk. The recognition that women with early reproductive decline constitute a population at increased vascular risk provides important opportunities for early intervention in terms of both risk factor modification and, when appropriate, hormonal treatment. Although additional research is needed to clarify the complex associations between accelerated reproductive aging and vascular health, applying current knowledge will help to reduce cardiovascular events in this high-risk patient population.

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References

1. Roger VL, Go AS, Lloyd-Jones DM, et al. American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics–2011 update: a report from the American Heart Association. Circulation. 2011; 123(4):e18–e209. [PubMed: 21160056]
2. van der Schouw YT, van der Graaf Y, Steyerberg EW, Eijkemans JC, Banga JD. Age at menopause as a risk factor for cardiovascular mortality. Lancet. 1996; 347(9003):714–718. [PubMed: 8602000]
3. North American Menopause Society. The 2012 hormone therapy position statement of: The North American Menopause Society. Menopause. 2012; 19(3):257–271. [PubMed: 22367731]
4. Stuenkel CA, Davis SR, Gompel A, et al. Treatment of symptoms of the menopause: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2015; 100(11):3975–4011. [PubMed: 26444994]
5. Muka T, Oliver-Williams C, Kunutsor S, et al. Association of age at onset of menopause and time since onset of menopause with cardiovascular outcomes, intermediate vascular traits, and all-cause mortality: a systematic review and meta-analysis [published online September 14, 2016]. JAMA Cardiol.
6. Kok HS, van Asselt KM, van der Schouw YT, et al. Heart disease risk determines menopausal age rather than the reverse. J Am Coll Cardiol. 2006; 47(10):1976–1983. [PubMed: 16697313]
7. Atsma F, Bartelink ML, Grobbee DE, van der Schouw YT. Postmenopausal status and early menopause as independent risk factors for cardiovascular disease: a meta-analysis. Menopause. 2006; 13(2):265–279. [PubMed: 16645540]
8. Manson JE, Chlebowski RT, Stefanick ML, et al. Menopausal hormone therapy and health outcomes during the intervention and extended poststopping phases of the Women's Health Initiative randomized trials. JAMA. 2013; 310(13):1353–1368. [PubMed: 24084921]
9. Hodis HN, Mack WJ, Henderson VW, et al. ELITE Research Group. Vascular effects of early versus late postmenopausal treatment with estradiol. N Engl J Med. 2016; 374(13):1221–1231. [PubMed: 27028912]
10. Mulrooney DA, Armstrong GT, Huang S, et al. Cardiac outcomes in adult survivors of childhood cancer exposed to cardiotoxic therapy: a cross-sectional study. Ann Intern Med. 2016; 164(2):93–101. [PubMed: 26747086]