Women and Ischemia Syndrome Evaluation (WISE)
Diagnosis and Pathophysiology of Ischemic Heart Disease
Workshop

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Session 4

1. Topic and Author

Vascular Effects of HRT
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2. Where we stand in 2002. Overview/rationale for inclusion of topic.

Many potential benefits of ovarian hormones, in particular estrogen, on the cardiovascular system have been identified and include antiatherogenic and vasodilator actions.[1] The mechanisms that have been identified are many and varied and include stimulation of endothelial cell nitric oxide,[2] inhibition of vasoconstrictor factors such as endothelin I[3] and L-type calcium channels[4] as well as effects on other pathways such as the angiotensin[5] and autonomic nervous systems.[6] Despite these potentially favorable vascular actions, recent clinical trials have not confirmed a cardiovascular benefit of HRT.

HRT and Blood Flow

Experimental studies have demonstrated that continuous conjugated equine estrogens (CEE) augment endothelium-mediated dilation and delay progression of atherosclerosis in animal models.[7-10] The animal findings on coronary blood flow have been confirmed in postmenopausal women. Infusion of different estrogens in women with CAD during cardiac catheterization has been shown to increase coronary blood flow in response to acetylcholine.[11-14] The role of endogenous ovarian hormones in modulating peripheral vasoreactivity has been investigated in premenopausal[15] and postmenopausal women.[16] Variations in endothelial function during the menstrual cycle suggests that ovarian hormones, at physiologic concentrations, have effects on vasomotor tone[15] and confirms similar findings with estrogen treatment.[17] Some of the acute rapid effects of estrogen that have been demonstrated can now be explained by recently discovered rapid nongenomic but plasma membrane estrogen receptor–dependent actions via cytosolic signaling systems, such as the mitogen-activated protein kinase cascade.[18]

Data on the vascular actions of progestins are scant, less clear, and more complex, since the effects of the interaction with estrogen must be taken into account. Progesterone relaxes coronary arteries in a dose-dependent manner.[19] The relaxing potencies of the different progestins in coronary arteries vary and depend on whether the vessel has been exposed to estrogen. Measurements of endothelial function in response to different progestins in healthy women have produced varying results.[20-23] Micronized progesterone[24] or medroxyprogesterone acetate (MPA)[20] added to estradiol did not attenuate the favorable effect of estradiol on endothelium-dependent vasodilation in postmenopausal women, whereas MPA did attenuate this effect in another study.[21] Similarly, premenopausal women treated with gonadotropin-releasing hormone agonists who were given “add-back” continuous oral estradiol and norethisterone acetate showed an improvement in flow-mediated brachial artery reactivity compared with women who did not receive HRT.[22]

HRT and Exercise-Induced Myocardial Ischemia

Because of the vascular relaxing effects of estrogen in vitro and in animals and its actions on vascular reactivity and coronary blood flow in humans, the potential effects of estrogen on myocardial ischemia have been investigated. Rosano and co-workers showed that 17β-estradiol also has anti-ischemic effects in postmenopausal women with CAD.[25] This effect was confirmed by Alpaslan and colleagues using different methodology.[26] Acutely administered estrogen was shown, with the use of coronary sinus pH measurements, to have an anti-ischemic action in menopausal women with CHD.[27] A small clinical trail demonstrated that 4 and 8 weeks of transdermal estradiol therapy significantly increased exercise time to myocardial ischemia.[28] When the effects of natural progesterone were compared with those of MPA, a beneficial effect of oral estradiol combined with transvaginal progesterone on exercise time to myocardial ischemia in menopausal women with coronary heart disease (CHD) was demonstrated. In contrast, oral estrogen plus MPA did not produce a significant improvement over estrogen alone.[29] Results of these studies suggest that the choice of progestin combined

with estrogen in women with CHD may be important.
Postmenopausal women with angina due to cardiac syndrome X have some benefit from transdermal estrogen, which may or may not be due to an anti-ischemic action.[30]
In summary, data from a variety of studies have provided strong evidence that estrogen and some progestins can act as anti–myocardial ischemic agents in menopausal women with proven CHD. Further studies are required to show whether estrogen alone or combined with progesterone has long-term beneficial effects in such women.

HRT in Women with Established Cardiovascular Disease

Protective effects of hormone therapy have been reported in numerous observational studies. Despite effects on blood flow and myocardial ischemia, clinical trials have not shown a benefit on cardiovascular endpoints either in postmenopausal women with or without prior CAD.
There are a number of possible explanations for these null results, the large clinical trials thus far have investigated combinations of CEE and MPA. One possibility is that the progestin used, namely MPA, negated the potential beneficial effect of estrogen early in the study. Biologic support for this possibility comes from reports that show a detrimental effect of MPA on the beneficial effects of CEE with regard to vascular reactivity[31;32] [21] and atheroma development.[8;33] Studies also show that progesterone does not appear to have this inhibitory effect either on atheroma development[34] or vascular reactivity in animal models[32] or on vascular reactivity[24] and exercise-induced myocardial ischemia in humans.[29]
It is possible that different estrogens at different doses and with different combinations of progestins may yield different results.

3. Current challenges and the most important issues for future research

Understanding the link between the obvious vascular actions of HRT and the disparity in the clinical trail data with regard to clinical cardiovascular events. Much of the clinical trial data are limited to a single HRT preparation. Are there differences in the vascular actions of different estrogens and progestins?

4. Current challenges in the areas of communicating messages to health care community, patients and the public

Greater awareness of the lifestyle changes that will reduce the risk of vascular disease.[35] Greater awareness and use of established cardioprotective pharmacological interventions by both the public and the medical profession.

5. Translating new findings to improved diagnosis and treatment/saving lives.

Clearly the emphasis has shifted away from HRT with regard to cardiovascular protection. Re-emphasis of established lifestyle changes and pharmacological interventions for the reduction in the risk of cardiovascular events should be encouraged.

6. References.

1. Mendelsohn ME,.Karas RH. The protective effects of estrogen on the cardiovascular system. *N.Engl.J Med* 1999;**340**:1801-11.
2. Chen Z, Yuhanna IS, Galcheva-Gargova Z, Karas RH, Mendelsohn ME, Shaul PW. Estrogen receptor alpha mediates the nongenomic activation of endothelial nitric oxide synthase by estrogen. *J Clin.Invest.* 1999;**103**:401-6.
3. Webb CM, Ghatei M, McNeill JG, Collins P. 17β-Estradiol decreases endothelin-1 levels in the coronary circulation of postmenopausal women with coronary artery disease. *Circulation* 2000;**102**:1617-22.
4. Collins P, Rosano GMC, Jiang C, Lindsay D, Sarrel PM, Poole-Wilson PA. Hypothesis: Cardiovascular protection by oestrogen - a calcium antagonist effect? *Lancet* 1993;**341**:1264-5.
5. Proudler AJ, Hasib Ahmed AI, Crook D, Fogelman I, Rymer JM, Stevenson JC. Hormone replacement therapy and serum angiotensin-converting-enzyme activity in postmenopausal women. *Lancet* 1995;**346**:89-90.
6. Vongpatanasin W, Tuncel M, Mansour Y, Arbique D, Victor RG. Transdermal estrogen replacement therapy decreases sympathetic activity in postmenopausal women. *Circulation* 2001;**103**:2903-8.
7. Williams JK, Adams MR, Klopfenstein HS. Estrogen modulates responses of atherosclerotic coronary arteries. *Circulation* 1990;**81**:1680-7.

8. Adams MR, Register TC, Golden DL, Wagner JD, Williams JK. Medroxyprogesterone acetate antagonizes inhibitory effects of conjugated equine estrogens on coronary artery atherosclerosis. *Arterioscler.Thromb.Vasc.Biol.* 1997;**17**:217-21.

9. Alexandersen P, Haarbo J, Sandholdt I, Shalmi M, Lawaetz H, Christiansen C. Norethindrone acetate enhances the antiatherogenic effect of 17beta-estradiol: a secondary prevention study of aortic atherosclerosis in ovariectomized cholesterol-fed rabbits. *Arterioscler.Thromb.Vasc.Biol.* 1998;**18 (6)**:902-7.

10. Haarbo J, Leth-Espensen P, Stender S, Christiansen C. Estrogen monotherapy and combined estrogen-progestogen replacement therapy attenuate aortic accumulation of cholesterol in ovariectomized cholesterol-fed rabbits. *J.Clin.Invest.* 1991;**87**:1274-9.

11. Reis SE, Gloth ST, Blumenthal RS, Resar JR, Zacur HA, Gerstenblith G *et al*. Ethinyl estradiol acutely attenuates abnormal coronary vasomotor responses to acetylcholine in postmenopausal women. *Circulation* 1994;**89**:52-60.

12. Gilligan DM, Quyyumi AA, Cannon RO, III. Effects of physiological levels of estrogen on coronary vasomotor function in postmenopausal women. *Circulation* 1994;**89**:2545-51.

13. Collins P, Rosano GMC, Sarrel PM, Ulrich L, Adamopoulos S, Beale CM *et al*. Estradiol-17β attenuates acetylcholine-induced coronary arterial constriction in women but not men with coronary heart disease. *Circulation* 1995;**92**:24-30.

14. Guetta V, Quyyumi AA, Prasad A, Panza JA, Waclawiw M, Cannon RO, III. The role of nitric oxide in coronary vascular effects of estrogen in postmenopausal women. *Circulation* 1997;**96**:2795-801.

15. Hashimoto M, Akishita M, Eto M, Ishikawa M, Kozaki K, Toba K *et al*. Modulation of endothelium-dependent flow-mediated dilatation of the brachial artery by sex and menstrual cycle. *Circulation* 1995;**92**:3431-5.

16. Volterrani M, Rosano GMC, Coats A, Beale C, Collins P. Estrogen acutely increases peripheral blood flow in postmenopausal women. *Am.J.Med.* 1995;**99**:119-22.

17. Lieberman EH, Gerhard MD, Uehata A, Walsh BW, Selwyn AP, Ganz P *et al*. Estrogen improves endothelium-dependent, flow-mediated vasodilation in postmenopausal women. *Ann.Intern.Med.* 1994;**121**:936-41.

18. Collins P,.Webb C. Estrogen hits the surface. *Nature Medicine* 1999;**5 (10)**:1130-1.

19. Jiang C, Sarrel PM, Lindsay DC, Poole-Wilson PA, Collins P. Progesterone induces endothelium-independent relaxation of rabbit coronary artery in vitro. *Eur.J.Pharmacol.* 1992;**211**:163-7.

20. Koh KK, Jin DK, Yang SH, Lee SK, Hwang HY, Kang MH *et al*. Vascular effects of synthetic or natural progestagen combined with conjugated equine estrogen in healthy postmenopausal women. *Circulation* 2001;**103**:1961-6.

21. Kawano H, Motoyama T, Hirai N, Yoshimura T, Kugiyama K, Ogawa H *et al*. Effect of medroxyprogesterone acetate plus estradiol on endothelium- dependent vasodilation in postmenopausal women. *Am J Cardiol.* 2001;**87**:238-40.

22. Yim SF, Lau TK, Sahota DS, Chung TK, Chang AM, Haines CJ. Prospective randomized study of the effect of "add-back" hormone replacement on vascular function during treatment with gonadotropin- releasing hormone agonists. *Circulation* 1998;**98**:1631-5.

23. Sorensen KE, Dorup I, Hermann AP, Mosekilde L. Combined hormone replacement therapy does not protect women against the age-related decline in endothelium-dependent vasomotor function. *Circulation* 1998;**97**:1234-8.

24. Gerhard M, Walsh BW, Tawakol A, Haley EA, Creager SJ, Seely EW *et al*. Estradiol therapy combined with progesterone and endothelium-dependent vasodilation in postmenopausal women. *Circulation* 1998;**98**:1158-63.

25. Rosano GMC, Sarrel PM, Poole-Wilson PA, Collins P. Beneficial effect of oestrogen on exercise-induced myocardial ischaemia in women with coronary artery disease. *Lancet* 1993;**342**:133-6.

26. Alpaslan M, Shimokawa H, Kuroiwa-Matsumoto M, Harasawa Y, Takeshita A. Short-term estrogen administration ameliorates dobutamine-induced myocardial ischemia in postmenopausal women with coronary artery disease. *J.Am.Coll.Cardiol.* 1997;**30**:1466-71.

27. Rosano GMC, Caixeta AM, Chierchia SL, Arie S, Lopez-Hidalgo M, Pereira WI *et al*. Acute anti-ischemic effect of estradiol-17β in

postmenopausal women with coronary artery disease. *Circulation* 1997;**96**:2837-41.

28. Webb CM, Rosano GMC, Collins P. Oestrogen improves exercise-induced myocardial ischaemia in women. *Lancet* 1998;**351**:1556-7.

29. Rosano GMC, Webb CM, Chierchia S, Morgani GL, Gabraele M, Sarrel PM *et al*. Natural progesterone, but not medroxyprogesterone acetate, enhances the beneficial effect of estrogen on exercise-induced myocardial ischemia in postmenopausal women. *J.Am.Coll.Cardiol.* 2000;**36 (7)**:2154-9.

30. Rosano GMC, Peters NS, Lefroy DC, Lindsay DC, Sarrel PM, Collins P *et al*. 17-beta-estradiol therapy lessens angina in postmenopausal women with syndrome X. *J.Am.Coll.Cardiol.* 1996;**28**:1500-5.

31. Williams JK, Honore EK, Washburn SA, Clarkson TB. Effects of hormone replacement therapy on reactivity of atherosclerotic coronary arteries in cynomolgus monkeys. *J.Am.Coll.Cardiol.* 1994;**24**:1757-61.

32. Miyagawa K, Rosch J, Stanczyk F, Hermsmeyer K. Medroxyprogesterone interferes with ovarian steroid protection against coronary vasospasm. *Nature Medicine* 1997;**3**:324-7.

33. Levine RL, Chen SJ, Durand J, Chen YF, Oparil S. Medroxyprogesterone attenuates estrogen-mediated inhibition of neointima formation after balloon injury of the rat carotid artery. *Circulation* 1996;**94**:2221-7.

34. Adams MR, Kaplan JR, Manuck SB, Koritnik DR, Parks JS, Wolfe MS *et al*. Inhibition of coronary artery atherosclerosis by 17-beta estradiol in ovariectomized monkeys. Lack of an effect of added progesterone. *Arteriosclerosis* 1990;**10**:1051-7.

35. Manson JE, Greenland P, LaCroix AZ, Stefanick ML, Mouton CP, Oberman A *et al*. Walking compared with vigorous exercise for the prevention of cardiovascular events in women. *N.Engl.J.Med.* 2002;**347**:716-25.