HORMONE REPLACEMENT THERAPY AND CARDIOVASCULAR DISEASE

Heart and Stroke Foundation of Canada
Society of Obstetricians and Gynecologists of Canada
Canadian Cardiovascular Society

In Canada cardiovascular diseases (CVD) are the leading cause of mortality. In 1999, CVD were responsible for 39,134 deaths among Canadian women (approximately 37% of all deaths in women), which is greater than the number of deaths for women due to all cancers combined. The proportion of deaths due to CVD in women increases significantly after menopause and continues to increase with advancing age. It remains unclear, however, whether this increase in incidence of CVD in middle aged and elderly women is caused by lower estrogen levels or is an overall manifestation of advancing age. The use of hormone replacement therapy (HRT), especially estrogen, has been advocated as a means to reduce the risk of CVD.

Menopause is associated with adverse effects on blood lipids including an increase in total cholesterol, LDL cholesterol, and triglycerides, and a decrease in HDL cholesterol. Reduced estrogen levels after menopause can also lead to adverse changes in blood pressure, obesity, body fat distribution, blood clotting factors, glucose metabolism and diabetes, all of which increase the risk of coronary heart disease.

Laboratory studies have found evidence for both beneficial and adverse effects of estrogen. Oral estrogen has been shown to lower LDL cholesterol, lipoprotein (a), and increase HDL cholesterol. There is accumulating evidence that estrogen improves endothelial function, thus enhancing vasodilatation. In addition, estrogen replacement is associated with reduced blood levels of fibrinogen and plasminogen activator inhibitor-1, and may thus have anti-thrombotic and pro-fibrinolytic effects. However, other effects may be pro-inflammatory (increased C-reactive protein) and pro-coagulant and therefore detrimental to the overall cardiovascular risk profile.

As estrogen is usually prescribed with progestin in those women with a uterus in order to protect against endometrial cancer, some of the beneficial cardiovascular effects may be attenuated by the addition of progestin (such as a lesser effect on HDL cholesterol). Other routes of administration of estrogen may have less favourable effects on plasma lipoproteins, but may be beneficial in other ways. Selective estrogen receptor modulators (SERMs) are also being studied because these may result in direct cardiovascular effects.

The evidence for a protective effect of estrogen against coronary artery disease is based on over 30 observational epidemiologic studies conducted over the last two decades. These studies have shown a 40% reduction in the risk of coronary artery disease for current users of estrogen or estrogen and progestin compared to women who have never used these hormones. Recent updates have confirmed this conclusion, even with lower doses of estrogen, but have also found no effect of HRT on stroke. However, these types of studies are hampered by an inability to control completely for confounding factors, including the fact that women who are compliant with HRT tend to be healthier. Randomized controlled clinical trials are considered to provide the strongest evidence for definitive conclusions concerning HRT and CVD outcomes.

The Heart and Estrogen/Progestin Replacement Study (HERS) was a randomized trial of secondary prevention using HRT in women with established coronary disease. The investigators did not find an over-all benefit after 4.1 years of treatment with combined estrogen and progestin. There was a significant increase in the risk of nonfatal MI or coronary death in the first year in women on active treatment (this risk lessened over the duration of the study) and an approximate three-fold increase in the risk of venous thromboembolic events. In order to determine if a benefit of HRT on CVD outcomes could be observed over a longer duration of follow-up, the HERS cohort was followed in an observational format for a further 2.7 years. HERS II did not find any benefit of the assigned HRT regimen in these women with coronary artery disease, although only 45% of women were still on HRT by the end of year 6. Another randomized trial using a similar regimen of HRT or estrogen alone and conducted in a similar group of women as HERS, the Estrogen Replacement and Atherosclerosis (ERA) trial, found no difference in the progression of coronary atherosclerotic disease using angiography as an endpoint. Furthermore, HRT did not reduce the risk of ischemic stroke in women with established coronary artery disease in HERS and HERS II. These findings were confirmed in a randomized controlled trial of 17 beta-estradiol in postmenopausal women with a previous history of stroke or TIA. After 2.8 years of treatment, there was no reduction in the risk of recurrent stroke.

Such randomized trials were conducted only in those women who already had evidence of coronary artery disease or stroke, whereas cohort observational studies such as the Nurses' Health Study included women who have no evidence of such disease. Consequently, there was debate as to whether results from secondary prevention trials could be extrapolated to HRT for primary prevention and whether other doses and/or routes of administration might prove effective.

Recently, one trial of the long-awaited Women's Health Initiative (WHI), involving 16,608 women with an intact uterus aged 50-79 years (mean age 63 years), reported the principal results. Although the trial was scheduled to be completed in 2005, the trial was stopped early, after 5.2 years of follow-up, based on an assessment of greater risk with HRT than benefit in this important study of primary prevention. Although its primary outcome was nonfatal MI and coronary death, the trial was stopped due to a small increased risk of invasive breast cancer (8 cases/10,000 women), a diagnosis that was a pre-determined primary adverse outcome and this excess risk increased with duration of treatment. For CVD, there was an increased risk (7 cases/10,000) of nonfatal MI and coronary death (especially within the first year of treatment, remaining neutral over the ensuing years). There was an excess risk of stroke (8 cases/10,000) which persisted throughout the trial, and a doubling of risk for venous thromboembolism. This translates into an increased relative risk of 22% of an adverse outcome for CVD with use of this HRT regimen and there was no statistical suggestion of potential benefit if the trial were to be continued. There was evidence of a benefit with respect to hip fractures (5 cases/10,000) and colorectal cancer (6 cases/10,000) but these outcomes did not result in an overall benefit for this treatment over the 5.2 years of the trial. Based on the duration reported in this trial, 100 more women per 10,000 on treatment will experience an adverse event. The excess risk is small but important given that this therapy has been advocated for prevention of disease. The WHI trial therefore does not support the use of this HRT regimen for the primary prevention of coronary artery disease. It should be noted that this trial did not evaluate women with menopausal symptoms nor those women with early or premature menopause. Another trial under the auspices of WHI is still in progress comparing unopposed estrogen to placebo in women who have had

hysterectomies. Interim analyses to date have indicated that the trial should continue until its planned termination in 2005.

Other effects of HRT besides those on the cardiovascular system must also be considered. The evidence linking unopposed estrogen to endometrial cancer is extensive, strong and consistent, however the addition of progestin in women with a uterus reduces this risk. A recent observational cohort study found that women who use estrogen-only HRT for a long period of time (10 years) have an increased risk of developing ovarian cancer. The unopposed estrogen arm of WHI may provide stronger evidence by 2005. As discussed above, WHI has shown an excess risk of breast cancer with continuous-combined HRT with longer duration of use. Any non-cardiovascular risks should be balanced with non-cardiovascular benefits, such as the treatment of menopausal symptoms and prevention of osteoporotic fractures and (possibly) colorectal cancer.

Coronary artery disease is the leading cause of death and an important contributor to morbidity and disability in women. It is largely preventable. Efforts should focus on reducing the risk of coronary artery disease among women in known and effective ways. Women should receive counseling about lifestyle modifications (smoking cessation, maintenance of a normal body weight, regular moderate to vigorous physical activity and consumption of a heart healthy diet) because of the important beneficial effects of these strategies. In addition, pharmacotherapy of hypertension and dyslipidemias should be utilized when indicated. For women who already have established heart disease, lifestyle modification including control of hypertension and diabetes assume heightened importance given their greater mortality associated with acute coronary events, such as myocardial infarction. Therapy with anti-platelet agents such as acetylsalicylic acid, beta blockers, angiotensin-converting enzyme inhibitors and lipid-lowering medications is recommended when indicated and is amply supported by evidence of benefit.

Based on current evidence, HRT should not be initiated or continued in women for the sole purpose of preventing future cardiovascular events, nor should it be used in the asymptomatic woman on a long- term basis. The previously discussed risks and non-cardiovascular benefits, patient preference, and treatment goals should guide any decision regarding the use of such therapy.

Dr. Beth Abramson
Dr. Christine Derzko
Dr. Andre Lalonde
Dr. Robert Reid
Dr. Michele Turek
Dr. Andreas Wielgosz

October 2002

BIBLIOGRAPHY

Mendelsohn ME, Karas RH. The protective effects of estrogen on the cardiovascular system. N Engl J Med 1999;340:1801-1811.

Herrington DM, Resboussin DM, Brosnihan KB, Sharp PC, Shumaker SA, Snyder TE, et al. Effects of estrogen replacement on the progression of coronary artery atherosclerosis. N Engl J Med 2000;343:522-529

Grodstein F, Manson JE, Colditz GA, Willett WC, Speizer FE, Stampfer MJ. A prospective, observational study of postmenopausal hormone therapy and primary prevention of cardiovascular disease. Ann Inter Med 2000;133:933-941

Hulley S, Grady D, Bush T, Furberg K, Herrington D, Riggs B, Vittinghoff E for the Heart and Estrogen/Progestin Replacement Study (HERS) Research Group. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. JAMA 1998;280:605-613.

Lenfant C. Statement from Claude Lenfant, MD, Director, National Heart,Lung,and Blood Institute, on preliminary trends in the Women's Health Initiative. National Heart, Lung, and Blood Institute Communications Office. 3 April, 2000

Stampfer MJ, Hu FB, Manson JE, Rimm EB, Willett WC. Primary prevntion of coronary heart disease in women through diet and lifestyle. N Engl J Med 2000;343:16-22.

Mosca L, Grundy SM, Judelson D, King K, Limacher M, Oparil S, et al. Guide to preventive cardiology for women. Circulation 1999;99:2480-2484.

Manson JE and Martin KA. Postmenopausal hormone replacement therapy. N Engl J Med 2001;345:34-40.

Grodstein F, Manson JE, Stampfer MJ. Postmenopausal hormone use and secondary prevention of coronary events in the Nurses' Health Study. A prospective observational study. Ann Intern Med 2001;135:1-8.

Mosca L, Collins P, Herrington DM et al. Hormone replacement therapy and cardiovascular disease. A statement for healthcare professionals from the American Heart Association. Circulation 2001;104:499-503.

McPherson R, Tardif JC, Jolly E. Hormone replacement therapy and cardiovascular disease. Can J Cardiol. 2001 Nov;17(Suppl D):32D-37D.

Turek MA, Derzko C. Hormone replacement therapy and cardiovascular disease. J Obstet Gynaecol Can 2001; 23(10):966-972

Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: Principal results from the Women's Health Initiative randomized controlled trial. JAMA. 2002:288:321-337.

Lacey JV, Mink PJ, Lubin JH, et al. Menopausal hormone replacement therapy and risk of ovarian cancer JAMA. 2002;288:334-341.

Grady D, Herrington D, Bittner V, et al for the HERS Research Group. Cardiovascular disease outcomes during 6.8 years of hormone therapy: Heart and Estrogen/progestin Replacement Study follow-up (HERS II). JAMA.2002;288:49-57.

Viscoli CM, Brass LM, Kernan WN, Sarrel PM, Suissa S, Horowitz RI. A clinical trial of estrogen-replacement therapy after ischemic stroke. N Engl J Med 2001; 345:1243-1249