CARDIOLOGY CASEBOOK
A regular feature of the American Journal of Critical Care, Cardiology Casebook is intended to enhance practitioners’ knowledge and critical thinking. Stylized case studies are accompanied by self-assessment quizzes. We welcome letters to the editors regarding this feature.

ESTROGEN PLUS PROGESTIN, BENEFITS AND RISKS: THE “WOMEN’S HEALTH Initiative” TRIALS

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The increase in coronary heart disease (CHD) in postmenopausal women continues unabated. Hormone replacement therapy given in an effort to contain this potentially fatal disease has had its successes and failures, but heretofore has not been fully evaluated. Hormone replacement therapy was first advocated in the 1940s for the treatment of menopausal symptoms. Subsequently several observational studies suggested cardiovascular benefits for women who were on hormone therapy. However no high risk clinical trials had been done until the early 1990s, when through the National Institutes of Health, 40 centers in the United States were recruited to enroll the largest number of postmenopausal women in a hormone study. The Women’s Health Initiative (WHI) was a large randomized placebo-controlled trial investigating the effects of estrogen plus progestin on specific potential long-term benefits versus risks. The Heart and Estrogen/progesterone Replacement Study (HERS), an “arm” of the WHI trial, was a randomly compared estrogen plus progestin trial given continuously to 16,000 women who were previously healthy and postmenopausal. A few women that were included in this “arm” had a history of coronary disease but had to have been asymptomatic for 6 months prior to enrollment. At the end of the study, there were no cardiovascular benefits and in fact, there was a significant increased risk in coronary events, primarily nonfatal myocardial infarctions, nearly 25% over 5+ years of follow-up. There was an increase in strokes, deep vein thrombosis, pulmonary emboli, and endometrial cancer. Breast cancer was a major risk after 4 years follow-up. An unusual finding was the increased requirement for gallbladder surgery. Two case presentations highlight key issues involved in hormone replacement therapy in women.

Case 1
A 61-year-old white woman was brought to the emergency department (ED) complaining of precordial chest pain. She had a history of hypertension, obesity, hyperlipidemia, and a maternal family history of cardiovascular disease (CVD). She was on antihypertensive medication (ie, a diuretic and an angiotensin-converting enzyme inhibitor), and had been on estrogen and progestin therapy since menopause at age 51. After an Internet search, the patient considered hormone replacement therapy to be protective from CHD and was not concerned about her blood lipids. Her home blood pressure averaged 135/80 mm Hg, but was 160/90 mm Hg in the ED. An electrocardiogram revealed ST depression in leads V1-V4; the cardiac troponin I levels were elevated. She had chewed and swallowed an adult aspirin tablet at home. The chest pain was relieved with 3 mg of intravenous morphine sulfate. In the ED prior to hospital admission, clopidogrel, enoxaparin, and abciximab were administered. On admission to the coronary care unit, she was given an oral β-blocker and a statin.

Question
1. Which of the following is/are true?
   a. CVD is the leading cause of death in the Western world
   b. men have a greater incidence of CVD than women
   c. estrogen and progestin replacement therapy decreases the incidence of CVD in postmenopausal women

Answer
1. a. CVD is the leading cause of death in the Western world
   b. men have a greater incidence of CVD than women

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It is well known that CVD is the leading cause of death in the Western world. In 1997, CVD accounted for more than 500,000 deaths in women in the United States alone. Premenopausal women have a much lower incidence of CHD than males in the same age group. However, after menopause, the incidence of CHD increases, and by the sixth decade the mortality rate due to CHD in women equates with that in men. These facts led many to postulate that endogenous production of estrogen would have a cardioprotective effect. This belief was enhanced by the clinical observation that the use of estrogen reduces blood lipid levels and by observational studies that reported a reduction of 30% to 40% in the risk of CHD in estrogen users (these studies were all nonrandomized and not double-blind). However, 2 large randomized studies published in 2002 have radically changed our concepts of the effects of hormone replacement therapy. The HERS II study was a randomized, blinded placebo-controlled trial on the effects of a combination of estrogen and progestin on CHD event risk among 2763 postmenopausal women with established CHD. This study concluded that after 6 to 8 years, hormone replacement therapy did not reduce the risk of cardiovascular events in women with CHD. The WHI trial enrolled 161,809 postmenopausal women (ages 50 to 79) in a trial of hormone replacement. The trial was stopped early when health risks were noted to exceed benefits over a follow-up of 5.2 years. The rate of coronary events, most of which were nonfatal myocardial infarctions, increased by 29% in patients receiving estrogen plus progestin when compared with patients receiving placebo.

Finally, this patient’s home blood pressures were reported to be 135/80 mm Hg. Currently this blood pressure is considered abnormal (American Heart Association guidelines) and should be lowered to 125 mm Hg systolic by adjusting antihypertensive medication. Attaining safe lipid levels to achieve a low-density lipoprotein (LDL) level of 70 mg/dL (1.81 mmol/L) or lower is mandatory in controlling atherosclerotic heart disease. The ideal blood levels that should be attained for the other lipids are a total cholesterol level below 200 mg/dL (5.17 mmol/L), triglycerides below 150 mg/dL (1.69 mmol/L), and high-density lipoprotein (HDL) above 55 mg/dL (1.42 mmol/L). Elevating HDL levels are the most difficult to achieve.

Case 2

A 54-year-old woman in good health presents for her annual physical examination. She has no complaints and had an unremarkable menopause at 48 years of age. A routine blood lipid profile revealed: total cholesterol 240 mg/dL (6.21 mmol/L), LDL 140 mg/dL (3.62 mmol/L), HDL 40 mg/dL (1.03 mmol/L), and triglycerides 175 mg/dL (1.98 mmol/L). A bone density test revealed mild osteoporosis. A combination of estrogen and progestin was prescribed to prevent an increase in osteoporosis.

Questions

2. Estrogen plus progestin replacement therapy increases the risk of developing which of the following?

   a. breast cancer
   b. endometrial cancer
   c. colon cancer
   d. venous thromboembolic disease

3. What other factors have been uncovered by the WHI trial?

   a. hormone replacement therapy reduces hip fractures
   b. hormone replacement therapy prevents CHD
   c. hormone replacement therapy lowers blood lipids
   d. birth control pills lower the risk of heart disease and strokes
   e. hormone replacement therapy reduces colon cancer

Answers

2. a. breast cancer
   b. endometrial cancer
   d. venous thromboembolic disease

Epidemiological studies have shown a significant increased risk of breast cancer in women on hormone replacement therapy. The WHI I trial was stopped after a mean of 5.2 years, when data indicated that there was a 26% increased incidence of breast cancer. Estrogen replacement therapy alone increases the incidence of endometrial cancer. The use of progestin in addition to estrogen reduces the risk of endometrial cancer substantially, but increases the risk of breast cancer.

Women in the WHI trial had a twofold rate of venous thromboembolic episodes. The HERS study found that in the first 90 days after a myocardial infarction, the risk of venous thromboembolism was greatly increased. This led the American Heart Association to recommend that women who are on hormone replacement therapy and have an acute cardiac event receive deep venous thrombosis prophylaxis (ie, enoxaparin subcutaneously) and/or discontinue hormone replacement therapy. The greatest risk of developing deep vein thrombosis is in the first year of hormone replacement therapy.
3.  
a. hormone replacement therapy reduces hip fractures 
b. birth control pills lower the risk of heart disease and strokes 
c. hormone replacement therapy reduces colon cancer

The rate of hip fractures is lower in the group receiving estrogen plus progestin therapy than in the placebo group. In fact, the overall rate of fractures in other bones was also significantly reduced. Thirty-three percent of women, compared to 8.3% of men, develop osteoporosis in their lifetime. Although bone loss begins around 40 years of age, the problem is exacerbated in the ages of 50 to 60 years, as a result of estrogen deficiency. Estrogen hormone replacement therapy prevents osteoporosis in women. Treatment is evaluated by bone mineral density measurements of the hip and vertebral bones. However, once hormone replacement therapy is stopped, the accelerated bone loss resumes. Hormone replacement therapy requires long-term use to maintain protection from fractures. However, the potential for an increase in coronary artery events has to be considered when advising this therapy for protection against osteoporosis. An unexpected finding was that hormone replacement therapy lowered the risk of colorectal cancer by 37%.

Recent preliminary reports from the WHI trial suggest that it may be the type of hormones and the life status when hormones are used that make them helpful at one point and harmful at another. In the United States, the most commonly prescribed hormone replacement therapy contains medroxyprogesterone acetate and conjugated equine estrogens, which are estrogens derived from horse urine. This form of estrogen contains a complex composition of 9 different estrogens, some of which do not even occur in humans. Whereas birth control pills contain 4 to 6 times the amount of estrogen as in hormone replacement therapy, the estrogen in birth control pills is synthetically derived and considered to be different from the estrogens used postmenopausally. This view has been enhanced by recent reports from the WHI trial that women who used birth control pills have had a lower risk of heart disease and stroke and no risk of breast cancer.

SUMMARY

Estrogen plus progestin should not be given to healthy postmenopausal women for the primary prevention of CHD. The substantial risk for cardiovascular disease should be weighed against the benefits for practical prevention in selecting from available agents to prevent osteoporosis. Nonetheless, hormone replacement therapy remains highly effective for menopausal symptoms. Ten to 20% of women find their menopausal symptoms intolerable. Many women consider the risks of hormone therapy (stroke, CHD, breast cancer, endometrial cancer, venous thromboembolic disease) acceptable in return for relief of menopausal symptoms. It is estimated that 1 serious adverse event will occur in 1000 50-year-old women using hormone replacement therapy for 1 year. Under these circumstances hormone therapy should be reassessed at yearly intervals and treatment readily tapered.

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