OPTIONS CENTER HEALTH TOPIC

Hormone Replacement Therapy Study Stopped

You may already be aware of the recent reports concerning the use of HRT and increased cardiovascular risks and ovarian cancer. These reports have confirmed and extended some of the concerns raised by the HERS (Heart and Estrogen/ Progestin Replacement Study) trial more than a year ago. The recent study can be located on JAMA's web site at: <http://jama.ama-assn.org/issues/v288n/ffull/joc21036.html.>

The clinical trial was stopped early based on the fact that the health risks were exceeding the health benefits over the first 5 years of the trial. To sum up the findings: women receiving HRT were 29% more likely to experience cardiovascular events, 41% more likely to experience strokes, 2-fold greater rates of deep vein thrombosis and pulmonary embolisms, and a 26% increase in invasive breast cancer over women in the placebo group. While HRT has a modest decrease in fractures (-24%) and both endometrial and colorectal cancers (-17% and 37%), these were not seen by the investigators to offset the risks. The following is a description of the HRT study.

The Estrogen plus Progestin Trial

On July 9, 2002, a press release indicated that the National Heart, Lung, and Blood Institute (NHLBI) of the National Institutes of Health (NIH) stopped a major clinical trial investigating the risks and benefits of combined estrogen and progestin in healthy menopausal women. The follow-up at 5.2 years, it was decided that the health risks outweighed the benefits. An independent data and safety monitoring board (DSMB) recommended stopping the trial because it found an increased risk of invasive breast cancer (the number of cases of breast cancer reached a pre-specified safety limit).

The study also found increases in coronary heart disease (CHD), stroke, and pulmonary embolism in study participants receiving the combined estrogen and progestin compared to women receiving the placebo.

The trial results and an editorial were published in the Journal of the American Medical Association (JAMA 2002; 288:322-333, 366-8) and are freely available from its website (www.jama.com) - go to the Past Issues section, July 17, 2002 link.

Study Features

In this randomized, placebo-controlled trial, which was a component of the Women's Health Initiative, 16,608 postmenopausal women aged 50-79 years with an intact uterus were recruited by 40 U.S. medical centers during 1993-1998. Participating women received conjugated estrogens (0.625 mg/day) plus medroxyprogesterone acetate (2.5 mg/day) combined in one tablet or placebo.

The study was designed to investigate the efficacy and safety of long-term hormone replacement therapy (HRT) in preventing diseases in postmenopausal women. It was not designed to

investigate the efficacy of HRT in alleviating menopausal symptoms. There were no substantial differences between the groups at baseline.

Outcome Measures: What Was Measured

Primary outcome	Coronary heart disease(CHD, nonfatal myocardial infarction and CHD death)
Secondary outcome	Hip fracture
Additional secondary outcomes	Other cardiovascular diseases
Primary adverse outcome	Invasive breast cancer

Results

On the basis of the statistical information obtained, the DSMB concluded that the evidence for breast cancer harm, along with evidence for some increase in CHD, stroke, and pulmonary embolism outweighed the evidence of benefit for fractures and possible benefits for colon cancer over the average follow-up period of 5.2 years.

After one year, 10,000 women taking estrogen plus progestin compared with the placebo might experience:

- 7 more CHD events (nonfatal myocardial infarction; there was no difference between the groups for death from heart attacks)
- 8 more strokes
- 8 more pulmonary embolisms
- 8 more invasive breast cancers
- 6 fewer colorectal cancers
- 5 fewer hip fractures

Endometrial cancer incidence, lung cancer incidence, death rate, and cause of death were not affected. The risk of an adverse event could actually be higher. Of the 16,608 who were enrolled in the trial, 583 women (231 receiving estrogen-progestin, 218 receiving placebo) were lost to follow-up or stopped providing information after 18 months. A substantial number of women had stopped taking the study drugs at some time (42% of estrogen + progestin; 38% of placebo) cumulatively by the seventh year. Some women in both groups initiated hormone use through their own doctor: 6.2% in the estrogen-progestin group, 10.7% in the placebo group cumulatively by the sixth year. (The participants had been enrolled for at least 3.5 years, with an average follow-up of 5.2 years.)

The study concluded that combined estrogen and progestin at the investigated dosage should not be initiated or continued for the primary prevention of CHD. In addition, the substantial risks for cardiovascular disease and breast cancer must be weighed against the benefit for fracture in selecting from the available agents to prevent osteoporosis.

NHLBI Recommendations

In light of the trial results, the NHLBI has recommended the following guidelines for estrogen plus progestin use:

- The therapy should not be continued or started to prevent heart disease. Women should consult their doctor about other methods of prevention, such as lifestyle changes, and cholesterol- and blood pressure-lowering drugs.
- For osteoporosis prevention, women should consult their doctor and weigh the benefits against their personal risks for heart attack, stroke, blood clots, and breast cancer. Alternative treatments are also available to prevent osteoporosis and fractures.
- Women should keep up with their regular schedule of mammograms and breast self-examinations.
- While short-term use was not studied, women taking the therapy for relief of menopausal symptoms may reap more benefits than risks. Women should talk with their doctor about their personal risks and benefits.

The Estrogen-Only Trial

Hot on the heels of the estrogen plus progestin trial, the National Cancer Institute released results of a trial studying estrogen alone. The study was also published in JAMA (JAMA 2002; 288: 334-341) although not freely available from its website.

Study Features & Outcome Measure

An observational study investigated the association between estrogen-only hormone replacement therapy and ovarian cancer. More than 44,241 postmenopausal women were included in the study which spanned approximately 20 years (1979-1998). The mean age at the start of follow-up was 56.6 years.

Results

Women who used estrogen-only HRT for 10 or more years had a significantly greater risk of developing ovarian cancer than women who did not use HRT. The risk increased with length of estrogen use.

Duration of Estrogen Use	Relative Risk
10-19 years	1.8
20 years of more	3.2
Means	
10-19 years	80% higher risk than non-users
20 years of more	220% higher risk than non-users

No increased risk of ovarian cancer was found for women using estrogen-progestin therapy. However, the author points out that only a few of the women studied in this category had used the HRT for more than four years, so there is not enough information to give a definite answer.
-Source Unknown
Information taken from JAMA 2002; 288:322-333, 366-8

A saliva test is available at Options that will determine estrogen levels. Call or email us to find out more.

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