

## **JAMA Report on Hormone Replacement Therapy**

The Journal of the American Medical Association (JAMA) published an article in July 2002 about the risks and benefits of hormone replacement therapy in postmenopausal women. The physicians of PAMF have prepared some information to address questions people might have regarding hormone replacement therapy and the JAMA article.

*Risks and Benefits of Estrogen Plus Progestin in Healthy Postmenopausal Women*  
JAMA 2002; 288:321-333

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### **How was the JAMA study conducted?**

Healthy postmenopausal women were randomly assigned to take a placebo versus two hormones in combination: *estrogen* (conjugated equine estrogens, or Premarin® ) plus *progestin* (medroxyprogesterone acetate, or Provera® ). Neither the women nor their doctors knew who was taking hormones and who was taking the placebo. The women were followed on average for more than 5 years and were monitored for clinical outcomes, including heart disease, stroke, blood clots, breast cancer, colon cancer, hip fracture and spine fracture. This study is part of the Women's Health Initiative, a large project of the National Institutes of Health.

### **What's new in this report?**

The careful design of the study and analysis strengthens the findings, compared with earlier and smaller studies. Large numbers of women were followed for 5.2 years on average (8,506 in the hormone group; 8,102 in the placebo group). The women in the two groups were similar in age and health status, so the outcomes can be attributed more confidently to the use of the medication rather than characteristics of the women.

Prior studies either examined smaller numbers of patients; studied those with specific medical conditions at the start of the study (such as heart disease); or did not randomly assign women to take the hormones but relied on comparing women who had chosen whether or not to take the hormones.

### **What's NOT new in this report?**

**None of the positive or negative clinical outcomes are different from what has been reported in various other studies.** But the high quality of this study makes the findings more compelling and obligates physicians and patients to reevaluate their decisions about using hormone replacement therapy.

### Why did this study generate such broad media attention now?

The study was intended to continue for 8.5 years. It was stopped in May 2002 because the number of breast cancers detected in the women taking hormones exceeded the warning threshold, and the overall risks of combined estrogen and progestin use exceeded the benefits.

### What are the main results of the study?

The women who took the hormones were more likely to experience heart attacks, strokes, other blood clots and invasive breast cancer. **The absolute increase in risk for each condition was small** (that is, the number of increased cases for each condition). Women taking hormones were significantly less likely to experience hip and spine fracture and colon cancer.

This table details the clinical outcomes, comparing the hormone and placebo groups, showing the frequency of each outcome *for every 10,000 "person years" observed*.

Outcome	Hormone	Placebo	Annual number of extra cases in hormone users, per 10,000 women	Annual number of fewer cases in hormone users, per 10,000 women
Coronary Heart Disease	37	30	7 more	--
Stroke	29	21	8 more	--
Other Blood Clots	34	16	18 more	--
Invasive Breast Cancer	38	30	8 more	--
Colon Cancer	10	16	--	6 fewer
Hip and Spine Fracture	10	15	--	5 fewer

### What other results were found?

1. A large number (42%) of women assigned to take hormones stopped doing so during the study. A small number (11%) of women assigned to take the placebo started taking hormones. Because of this crossover, the results may underestimate the effects of hormones in causing the outcomes seen, both positive and negative.
2. Overall death rates were similar between the hormone and placebo groups.
3. Short-term use of hormones (that is, less than 5 years) was not uniformly safer than longer-term use. Differences in several outcomes (such as coronary heart disease and stroke) between the hormone and placebo users developed soon after the study began.

## **Are there any other studies coming out that might refute these findings?**

We cannot predict the results of any future studies being conducted. But the Women's Health Initiative study is the first randomized controlled trial of large numbers of women comparing hormone replacement and a placebo.

## **Unanswered questions**

1. What about the effects of hormone replacement on other conditions?

Researchers plan future reports on the effect of hormone use on gall bladder disease, diabetes, cognitive function and quality of life.

2. Which hormone is causing the outcomes: the estrogen, the progestin or both?

We do not know whether the outcomes seen are from the estrogen, the progestin or a combination of the two. Another arm of the study is continuing until 2005, examining women without a uterus who took estrogen alone versus a placebo. This may help suggest whether estrogen or progestin is responsible for the findings presented here.

3. What about other estrogen and progestin medications?

This study evaluated only one kind of estrogen and one kind of progestin, in a set dose for each. We do not know if these results will apply to different doses of the same medications or to other estrogens (such as ethinyl estradiol, or Estrace® ) or other progestins (such as norethindrone). We also do not know whether the results would vary according to how the drugs are taken: orally, through the skin, or through an intrauterine device (IUD).

## **What should patients do who are currently taking hormone replacement therapy (HRT)?**

**There is no reason to panic.** As we have always recommended, take the time to consider why you are taking HRT, for what symptoms or preventive concerns, based on your own health and family history. Then consider how you feel about the evidence presented, and how you feel about the balance of the risks and benefits of HRT.

1. If you are taking HRT for menopause symptoms (such as hot flashes, vaginal dryness, sleep disturbance or irritability), you may want to: continue using HRT in the short term, lower your dose, stop HRT for a while, or switch to other types of drugs that may help your specific symptoms.
2. If you are taking HRT to prevent heart disease or osteoporosis, this is a good time to rethink your options. Other medications and lifestyle improvements, such as maintaining normal body weight and cholesterol level, insuring adequate calcium and vitamin D intake, exercising regularly and avoiding tobacco, can decrease your risk of heart disease and osteoporosis.
3. If you decide to stop HRT on your own, there is no single best or safest way to do this. You may want to taper off slowly to note your reaction. You may wish to decrease the number of pills you take gradually, eliminating one or two pills each week until you are

off entirely; or alternating days of taking pills, one day on and one day off for several weeks. It is OK to stop abruptly, but do note that hot flashes or other menopause symptoms may occur promptly after stopping or may gradually increase.

**Please let us know if you decide to stop HRT, so we can help you plan appropriate screening tests and monitoring to make sure you stay healthy and strong. As always, please discuss your concerns and decisions with your physician.**