Hormone Replacement Treatment

What is the controversy?

The WHI is a large government funded research program to study hormone replacement therapy It involves 16,608 postmenopausal women recruited from 1993 - 1998. A portion of the study was prematurely halted due to findings of increased risk of breast cancer, heart attack, stroke, and blood clots were published in JAMA on July 17, 2002. Participants in the WHI Hormone program that were in the study arm taking "estrogen plus progestin" have received written communication instructing them to stop taking their hormone study pills.

What were the study groups?

The WHI study involved two groups. The first group tested estrogen plus progestin in women who had not had a hysterectomy. The other group used estrogen alone in women who already had a hysterectomy. The "estrogen alone" study group will continue. Problem findings only involved those taking the estrogen plus progesterone. It is important to note that the adverse results pertain only to women taking combined continuous conjugated equine estrogen (Premarin 0.625 mg per day) and medroxyprogesterone acetate (Provera or Cycrin 2.5 mg per day). Another name for the medication is Prempro.

What were the findings of the WHI study?

Results indicate that during one year, for every 10,000 women taking "estrogen plus progestin," we would expect:

- 😐 7 more women with heart attacks compared to sugar pills - 37 versus 30
- 😐 8 more women with strokes - 29 versus 21
- 😐 8 more women with invasive breast cancer - 38 cases versus 30
- 😐 8 more women with blood clots in the lungs - 16 versus 8

- ☺ Results also suggest that there were beneficial effects such as:
- ☺ 5 fewer women would have hip fractures - 10 versus 15
- ☺ 6 fewer women would have colorectal cancers - 10 versus 16

As you can see the chance of something adverse happening to an individual taking her Prempro is very small, less than a tenth of 1 percent per year. Statistically, when you count all adverse events over the 5.2 years of the trial, the increased numbers of adverse events in the Prempro group was 100 per 10,000 (or 1 in 100 women). This small increase demonstrates that the risks probably add up over time.
The decision to stop the trial after 5 years of follow-up was made whei~th ese results met predetermined levels of harm. Most adverse outcomes began appearing within 1 to 2 years, but increased breast cancer risk did not show until year 3. Risk for stroke and venous blood clots continued throughout the 5 years of therapy. It appears in the second year of the study and is not explained by risk factors such as high blood

pressure, age, race, or ethnicity. It is interesting to note that the elevated risk of a heart attack was largely limited to the first year of therapy.

Study Analysis

- 😐 The study is the largest, most statistically valid, and well-analyzed research to evaluate the use of HRT in healthy postmenopausal women.
- 😐 Conclusions from this study can be applied reasonably only to Prernpro (or continuous Prernarin plus Provera).
- 😐 It's unclear whether reported effects are similar for other hormone replacement regimens that differ in dosage, preparation, or delivery method.
- 😐 Women taking HR'T should be made aware of the reported increased risks.
- 😐 There is no reported increase risk of breast cancer in the estrogen-only arm of the study.

The statistical analysis in the current WHI study appears strong and valid.

Cardiovascular Disease

- 😐 Women on Prempro had a 22% increase in cardiovascular disease and a 29%
- 😐 increased risk of coronary heart disease.
- 😐 The absolute increased risk for individual women is small but cumulative over time.

Breast Cancer

- 😐 There is a 26% increased risk of invasive breast cancer.
- 😐 The rates of breast cancer in the study population increased over time at a faster rate than would be explained by an increase in a woman's age alone.
- 😐 The individual increased risk is small but cumulative over time.
- 😐 Breast cancer takes several years to develop and in this trial it became clinically
- 😐 apparent at four years.

Stroke and Pulmonary Embolism

- 😐 There was a 41% increased risk of stroke and more than a two-fold increased risk of pulmonary embolism.
- 😐 'The absolute risk to individual women is low but cumulative over time.

Fractures

- ☺ Rates of hip fractures were reduced 34%.
- ☺ The WHI study is the largest study to date demonstrating the protective effect of HRT on hip fractures AND total fractures.

Colon Cancer

- ☺ The study suggests a benefit in the prevention of colorectal cancer with Prempro.

Recornmendations for Hormone Replacement Therapy Use

The decision about use of HRT requires evaluation of the risks and benefits for each individual woman. For women currently using HRT, it is important to assess their reasons for use and to evaluate potential risks, benefits, and alternatives. There is no data from the study to define what constitutes safe "short-term" use. The increase in diagnosis of invasive breast cancer appears after four years of use, but the influence of continuous estrogen and progestin therapy on breast cancer is unclear after even one year of use due to the biology of breast cancer.

Women who take HRT for hot flashes should be encouraged to take it for as short a time as possible and use the lowest effective dose. Long-term use of continuous combined estrogen and progestin therapy should be discontinued in asymptomatic patients. Patients interested in HRT for long-term use (e.g. quality of life issues) should be counseled about the risks and benefits of use, and about available alternatives. For women with a uterus, it is not recommended to go on estrogen alone due to increased risk of uterine cancer.

Combined continuous estrogen and progestin therapy is no longer recommended for the prevention of cardiovascular disease, and if previously prescribed for that purpose should be stopped. Alternatives for improved cardiac health include a healthy lifestyle (weight management, exercise, smoking cessation, use of blood pressure medications and cholesterol- lowering agents).

Alternatives to HRT for treatment of hot flashes include certain antidepressants, clonidine, soy protein, plant phytoestrogens, Bellergal-S, black cohosh and other agents. Osteoporosis can be prevented and treated by biphosphonates (Fosomax, Actonel) and SERMs (Evista).

Consider local therapy for genitourinary symptoms (dry vagina, incontinence). Options include estrogen vaginal cream or tablets. These methods do not increase blood estrogen levels much but there is little information on their long-term safety.
In general, patients should use the lowest dose of HRT that provides relief of symptoms.

Periodic reassessment of the need for HRT is recommended at least yearly. For women planning to stop their hormones, there are no definitive data to guide this process. Patients should be advised that stopping HRT might result in vaginal bleeding and hot flashes. If symptoms do occur, more gradual withdrawal should be considered.