

Lesson for Spine Research

The Controversy over hormone replacement therapy (HRT) provides the ultimate evidence that important medical treatments—including therapies for spinal problems should be evaluated in randomized controlled trials (RCTs) early in the research process.

It took nearly a third of a century to organize randomized trials to evaluate the claims that hormone replacement is a safe therapy with myriad benefits.

Three decades of observational studies had suggested that hormone replacement might protect women against heart disease, cancer, declining bone density, mood problems, and the symptoms of menopause. It took only a single, large RCT to raise questions about many of the claims of HRT proponents.

On May 31, The Women’s Health Initiative prematurely ended the 16,608-woman RCT comparing estrogen/progestin (Prempro, Wyeth) to placebo. Hormone replacement therapy caused a significant increase in the relative risk of heart disease (29% increase), invasive breast cancer (26% increase), stroke (41%), and pulmonary embolism (113%). While HRT appeared to provide benefit in terms of the relative risk of hip fractures (34% decrease) and colorectal cancer (37% decrease), the potential harm to subjects caused the organizers to shut the study down.

“Overall health risks exceeded benefits for use of combined estrogen plus progestin for an average 5.2 year follow-up among healthy post-menopausal US women...The risk-benefit profile found in this trial is not consistent with the requirements for a viable intervention for primary prevention of chronic diseases, and the results indicate that this regimen should not be initiated or continued for primary prevention of coronary heart disease,” according to the principal investigators. (See Women’s Health Initiative Writing Group, 2002)

“The whole purpose of healthy women taking long-term estrogen/progestin therapy is to preserve health and prevent disease,” according to an editorial by Susanne Fletcher, MD, and Graham Colditz, MD, at JAMA.com. “The results of this study provide strong evidence that the opposite is happening for important aspects of women’s health...”(See Fletcher and Colditz, 2002).

Risks and Benefits of Estrogen/Progestin in the Woman’s Health Initiative Randomized Controlled Trial*		
Disease	Change in Relative Risk for Subjects Taking Estrogen/Progestin	Absolute Risk per 10,000 Person-Years of Estrogen/Progestin Therapy
Coronary heart Disease events	29% increase compared to subjects taking placebo	7 more coronary events
Breast Cancer	26% increase	8 more invasive breast cancers
Stroke	41% increase	8 more strokes
Pulmonary Embolism	113% increase	8 more pulmonary emboli
Global Index Of Harm**	15% increase	N/A
Hip Fracture	34% decrease	5 fewer hip fractures
Colorectal Cancer	37% decrease	6 fewer colorectal cancers
* Study compared estrogen/progestin to placebo		
** A predefined measure of overall risk		
<i>Adapted from Woman’s Health initiative Writing Group, 2002.</i>		

Advice for Clinicians From Accompanying *JAMA* Editorial

- Clinicians should stop prescribing estrogen/progestin (Prempro) for long-term use.
- The absolute risk to an individual woman from estrogen/progestin therapy is small.
- Short-term use of estrogen/progestin to manage menopausal symptoms carries a small increased risk for coronary heart disease and thromboembolic disease.
- Women should consider other prevention options for heart disease, cancer, and osteoporosis.

(See Fletcher and Colditz, 2002.)

No Need for Despair

Women who are currently taking HRT in the form of estrogen/progestin should not shudder in fear over these findings. Although there were substantial increases in relative risk, the increases in absolute risk of heart disease, cancer, stroke, and pulmonary embolism were exceedingly modest.

Overall, there were seven more coronary heart disease events, eight more strokes, eight more pulmonary emboli, and eight more invasive breast cancers per 10,000 person-years of estrogen/progestin use. The absolute health advantage was also modest. There were only six fewer colorectal cancers and five fewer hip fractures per 10,000 person-years of therapy.

Some women may want to continue taking HRT in spite of the small increase in risk. “For some women, a short course or hormonal support is deliverance from some very unpleasant symptoms and worth the relatively small risks for a defined period of time,” says Susan Hall, MD, of Markdale, Ontario.

Some researchers have even questioned whether the risk estimates in this study are accurate. Nortin Hadler, MD, of the University of North Carolina suggests that it is impossible to attribute the handful of adverse events to the hormone therapy, given the possibility of randomization error and unknown confounders in this large and varied group of women. (See additional comments by Hadler on page 96).

Betrayal of Women's Interests

One could argue that the way the medical community has investigated HRT over the years has betrayed women's health interests. The medical community overvalued the claims of proponents and marketers, as well as the findings of observational studies that were incapable of proving the efficacy of HRT in disease prevention.

The medical establishment was slow to demand randomized trials. As a result, a third of a century into HRT, not a single RCT has been completed.

In an ideal world, the first randomized trial of hormone replacement should have been completed around the time of the first moon landing. There should have been multiple RCTs at this point--investigating a variety of hormone formulations for a variety of indications. It would appear that only one other major RCT on HRT is underway at this point. The other Women's Health Initiative RCT comparing estrogen alone to placebo for women who had hysterectomies is continuing.

Sadly, the evidence from the abandoned RCT may discourage further RCTs. It is much easier to organize RCTs when both patients and their doctors are in "equipoise" about the treatments being investigated.

Women were put at unnecessary--risk and then cast adrift--by this research process. Millions of women have been taking Prempro every day (22.3 million prescriptions in the United States alone every year) in the hopes of forestalling the effects of aging. Millions take other hormone formulations. They will now have to re-examine their options.

Uncertain Options

Although there are alternatives to HRT for the prevention of several diseases, there is no "all-in-one" disease prevention elixir. It would appear that women will have to analyze the risks and benefits of various approaches to prevention for several diseases individually; osteoporosis, coronary heart disease, breast cancer, and stroke, to name a few. These analyses will require complex risk/benefit decisions.

There is a larger issue here as well. To some extent, medicine and society have medicalized aging in women (and in men)--offering a negative and alarming view of normal age-related changes. Hormone replacement was a product of that process--an attempt to turn back the years and keep women "young." Some women may want to rethink society's view of aging as they ponder their therapeutic options.

Needless to say, the research process on HRT has also betrayed clinicians who treat menopausal women. Who would like to be a menopause specialist around now? Phones have been ringing off the hook at many clinics, as women desperately seek advice about therapy decisions. Some specialists are describing this turn of events as the worst shock in their professional careers.

REFERENCES:

Fletcher S and Colditz G., Failure of estrogen plus progestin therapy for prevention, *JAMA*, 2002; 288(3):366-8; jama.ama-assn.org/issues/v288n3/ffull/jed20042.html.

Women's Health Initiative Writing Group, Risks and benefits of estrogen plus progestin in healthy postmenopausal women, principal results from Women's Health Initiative Randomized Controlled Trial, *JAMA*, 2002;288(3):321-33; jama.ama-assn.org/issues/v288n3/ffull/joc21036.html.