

## newsletter

# Hormone replacement therapy

**The most extensive hormone replacement study to date terminated prematurely in May 2002 when it was discovered that the therapy increased the risk of breast cancer and heart attack. The study involved 16,608 post-menopausal women: one group received an estrogen-gestagen combination; others received placebos.**

### Introduction

Research on sex hormones began in 1923, with the first hormone product coming on the market soon after. Since that time, conjugated estrogens have come to be widely used. In Germany alone, the number of women over 45 who take hormones to ease menopausal complaints is estimated at 4.5 million. German physicians prescribed approximately one billion daily doses of hormones in 2000.

### Menopause, hormone replacement therapy (HRT)

In contrast to the male organism, which only gradually reduces its hormone production with advancing age, a woman's secretion of estrogen falls much more abruptly after menopause – the last spontaneous menstruation. The rapid decrease of estrogen in the bloodstream can provoke peri- or postmenopausal symptoms ranging from hot flashes, night sweats and mood swings to serious depression. Another problem specific to lower levels of estrogen in the blood is osteoporosis, which affects over 80% of menopausal women. To avoid or alleviate these menopausal symptoms, women have been treated for over 30 years with female sex hormones. The administration of estrogen/gestagen is known as hormone replacement therapy, or HRT.

### Results of the WHI (Womens Health Initiative) long-term study

The most extensive long-term study to date, of 16,608 postmenopausal women in the US, was begun in 1992 in the hope of demonstrating that HRT would protect women against heart attack and breast cancer. Roughly half of the test participants (8,506) received a preparation containing conjugated estrogen and a gestagen (medroxyprogesterone acetate, MPA); the other half received placebos. The US National Institute of Health (NIH) stopped this study after five of the projected nine years, as breast cancer and heart attacks were more common among the group receiving the estrogen/gestagen combination than among the placebo group (JAMA 2002, 288, 321-333). Subgroup analyses of women with and without histories of heart disease showed the same relative risk for cardiovascular events. In both cases, the risk was 29% higher than for the placebo group. The authors of the study report that the cardiovascular events were not significantly influenced by age, ethnicity, weight, earlier HRT, smoking, blood pressure, the intake of statins or aspirin, or diabetes mellitus. The conclusion was that in this respect, no group benefited from HRT.

Statistics also showed that the group receiving hormones had a 26% relative increase in the rate of breast cancer over the placebo group.

A second part of the WHI study investigated the effect of single-hormone therapy on 11,000 women who had undergone hysterectomy, with one group receiving conjugated estrogens and another receiving placebos. Interim results from this study have shown neither risks nor benefits; the study is to be continued into 2005. Whether this part of the study will show results similar to the combined therapy remains to be seen.

## **Conclusions**

The first part of the WHI study, of generally healthy postmenopausal women, was terminated prematurely because the risks (particularly of cardiovascular disease) among those receiving the combined hormone therapy were greater than the benefits. It demonstrated that combined estrogen-gestagen therapy for the prevention of cardiovascular disease, as practised in the US, is ineffective. The estrogen-gestagen preparations on the German market are approved as a preventive against osteoporosis and for substitution therapy during menopause, but not for the prevention of coronary heart disease.

The WHI study was able for the first time to furnish concrete figures on the prevention of osteoporosis. Those women receiving hormones had one third fewer bone fractures than those in the placebo group. However, considering the heightened occurrence of breast cancer and heart disease, the use of hormones to prevent osteoporosis must be questioned.

Their use for a reasonable period against menopausal complaints such as hot flashes and mood swings is still considered permissible. The effects of single-hormone estrogen therapy on the clinical end points named above will be demonstrated by the remaining part of the WHI study, scheduled to issue its next interim evaluation in 2003.

## **Information for the underwriter**

For insurance companies, the greatest risks in this context lie in the area of product liability (particularly recall covers) and in medical malpractice.

In the US, class action lawsuits are already being prepared on behalf of women who believe that their health has been impaired. If the relationship of risk to benefit proves to be unfavourable in other parts of the study as well – especially for single-hormone therapy – recalls may result. Thus, numerous frequently prescribed hormone preparations may be subject to similar risks. The high number of daily doses and the fact that side effects are often recognised only after years have elapsed aggravates this risk potential.

Medical malpractice covers may be affected if, for example, preparations were prescribed for therapies for which they were not approved. This case may even apply to preventive hormone treatment. Particularly critical are cases where a preparation was taken over several years.

Developments in this area should be carefully monitored in any event.

## **Contact**

AssTech GmbH  
Postfach 1211  
85766 Unterföhring bei München  
Telephone + 49 89 3844-1585  
Telefax + 49 89 3844-1586  
info@asstech.com  
www.asstech.com