HRT : RISKS & BENEFITS

Introduction

It is important to realize that **absence of detectable effects does not mean that there is no effect** : the effect might not have been picked up by the method used. This is not always realised when result are discussed.
It is generally wrongly **assumed that effects of menopause are reversible**. For osteoporosis it is well recognized that bone loss is not fully reversible after it has occurred. We have no arguments not to believe that the same might hold true to som extend for all the other effects. Unfortunately we do not have data, but if true, all studies involving patients whihc have been without hormones for longer periods might not be representative for those women who start therapy immediately after menopause

Quality of life

Vasomotor symptoms

men_hrt_vaso1.jpg Flushes and night sweats occur in most women after menopause, although the severity may vary. They generally disappear spontaneously after 3-4 years. Flushes and night sweats are effectively treated by estrogens.

- In general low doses of estrogens are sufficient to treat vasomotor symptoms.
- the effect depends on the dose : most of women are relieved with plasma concentrations of 100 pgr/ml but some require up to 200 pg/ml.
- it takes 3 months to obtain the full effect

Brain effects

men_hrt_vaso2.jpg Relief of vasomotor symptoms can be considered brain effects together with the effects on dizziness, depression, sleep etc.
Oestrogens clearly increase in animals synaptic density and transmission speed innerve cells. Oestrogens increase cerebral blood flow and in general have neuroprotective effect. It is unclear how these observations should clinically be translated. The available evidence on memory, brain function, and Alzheimer ranges from definite improvement to absence of detectable effect. It is important (1) to realize that absence of detectable effect does not mean that there is no effect –it might have been missed-, and (2) that to the best of my knowledge no negative effects have been described.
In addition ‘a mental tonic effect’ has been described although this effect is difficult to measure and to proof beyond doubt. It is generally accepted that for a mental tonic effect estrogen concentrations similar to those of a normal menstrual cycle are required.
men_alz2+1.jpg

Sexuality

Improved sexuality has been clearly demonstrated for almost all parameters investigated such as frequency, satisfaction, orgasm etc

Osteoporosis

men_osteo2.jpg Bone mass is is maximal around 35 years of age and decreases slowly thereafter. After menopause some 30% of women have accelerated bone loss : the so called rapid bone losers. These women if not treated will loose soo much bone that at age 70, 15% or more will have a fracture of hip, wrist or verterbrae.
Treatment with estrogens will completely prevent this accelerated bone loss, something what cannot be achieved by any other treatment. This has been observed in all studies, both epidemiological and RCT

- small doses of estrogens are sufficient to achieve this
- calcium intake (more than 800 mg/day) is important at all ages to maximise bone mass
- vitamin D also can prevent some bone loss
- only estrogens can completely prevent bone loss

During life bone is continuously remodeled with bone resorbtion and bone reformation. Two types of bone exist

- Trabecular bone eg vertebrae. During bone loss after menopause trabeculae get thinner and get lost : once integrity of trabeculae is lost continuity cannot be restored.
- Compact bone eg long bones. Bone loss occurs at the inside whereas bone formation occurs at the outside : therefore fingers become thicker with age.

Skin and Collagen

men_skin1+2.jpg It is well established that skin thickness increases with oestrogen therapy : this increase is dose dependent and it takes some 6 months before a full effect is reached. Skin thickness reflects the collagen layer together with collagen quality.
Is is unknown, although logical, what the relationship is between skin thickness and wrinkles and whether women taking HRT look younger througn increases in skin collagen/thickness.
Overall the correlation between skin thickness and bone mineral content is soo strong that is has been postulated that the decrease in collagen is causally related to the development in osteoporosis.

Pain of muscles and joints

men_osteo1.jpg Following menopause, some women experience muscle and bone pain which is relieved by taking HRT. Joints mostly affected are listed.

Cardiovascular

Cardiovascular accidents as stroke and myocardial infarction, are a source of controversy.

Epidemiologic studies .

Men_card3 Men_card2 All epidemiologic studies today invariably found **a 50% decrease in CVA's**. This observation was also made in women with diabetes. Based

upon the prevalence in society, this lead to the conclusion that in HRT users **mortality should be decreased by some 300 women/100.000 users/year**.
These studies have the advantage that all types of women, younger and older, lean or obese and all types of treatment were included. The criticism, however, is that a **population bias** cannot not be excluded ie that women taking HRT are overall healthier than those not taking HRT, and that this could explain the favourable effects.

Randomised clinical trials

Two larger randomized clinical trials have been performed
The HERS study aimed at the demonstration of a secondary prevention with combined HRT. The study was inconclusive after 4 years, with an increase in CVA the first year and a progressive decrease thereafter.
The WHI trial was equally inconclusive : a slight but not significant increase in CVA's was found. In 18000 women after 4 years .. versus .. CVA were found.
The main criticism on these trials is the extrapolation of the results : in the WHI study, 18.000 out of 180.000 women invited actually participated. In order to prevent early recognition of the active and placebo group, women with few complaints were selected. Hence it is not surprising that the group of women included in the study was older (mean 68 years), severely overweight (70-95 kilo) and had never taken hormones before. This is such a selected group, that extrapolation to younger, thinner women with complaints and starting early after menopause, can be considered purely speculative.

Conclusion

Both epidemiologic studies and RCT suffer from severe biases , the former from a population bias, the latter from selection biases. The answer probably lies somewhere in between the 2 results, ie a decrease or no effect. What the WHI trial clearly showed is that women at risk for CVA indeed have more CVA. This implies individualization of therapy, something that every clinician will take into account.
The heated discussions concerning CVA and HRT should be put in perspective.

- It can be considered as a statistical discussion : epidemiology versus RCT, each having specific advantages and disadvantages.
- It can be considered as HRT versus HT, as replacement therapy versus preventive medicine.
- From a gynaecological point of view, and from a replacement point of view, HRT is given for a series of reasons of which wellbeing and osteoporosis/collagen are the most important. If in addition a decrease in CVA is observed, this is a premium, if not, it is a pity, but not a reason to withhold HRT

Breast cancer

Prevalence

Although in the 80's a decrease in breast cancer prevalence was described all larger and more recent studies report an increased prevalence with an odds ratio between 1.35 (meta-analysis of epidemiologic studies) and 1.25 (WHI). Moreover the prevalence increases with the duration of intake.

Whether the effect of oestrogen and oestrogen-progestagen intake are different or not still is a matter of debate.

Accelerated growth versus induction.

Oestrogens clearly accelerate growth of breast cancer. It should be understood that acceleration of growth by definition will increase the apparent prevalence in any RCT. Today there is no evidence, to the best of my knowledge, that estrogens or progestagens will induce breast cancer : an existing breast cancer on the other hand will grow faster.

Accelerated growth : A benefit or a risk ?

Accelerated growth will automatically lead to an earlier diagnosis. Moreover data suggest, although not completely consistent ie varying from no effect to the following effects, that these breast cancers are of a less malignant, ie more estrogen receptor positive and that there are less metastasized. This leads to the presumption that type mortality will range from less to no effect

Adenocarcinoma

Other

Colon cancer