ELSEVIER

Maturitas 38 (2001) 235–237

MATURITAS
THE EUROPEAN MENOPAUSE JOURNAL

www.elsevier.com/locate/maturitas

Critical Comment

# The *Queen*… is naked!

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The last review of the Nurse's Health Study, with a follow-up from 1976–1996, published by F. Grodstein et al. [1] is a major contribution to evaluate the role of postmenopausal hormone therapy in the primary prevention of cardiovascular diseases. Again, the AA confirm that, 'the risk for major coronary events was lower among current users of hormone therapy, including short-term users, compared with never users (relative risk, 0.61 [95% CI, 0.52–0.71])'. However, 'the risk of stroke was statistically significantly increased among women taking 0.625 mg or more of oral conjugated estrogen daily'.

Surprisingly, a reanalyses of the HERS Study [2] concludes that in this population 'hormone therapy with conjugated equine estrogen and progestin had no significant effect on the risk for stroke among postmenopausal women with coronary disease'... After analyzing the data, the HERS team found that the, 'estrogen-progestin therapy did not significantly increase or decrease the risk of strokes or transient ischemic attacks. Nor did the therapy affect the risk of either ischemic or hemorrhagic strokes when examined separately'.

In an Editorial of the same Journal Tolbert and Oparil [3] advise that, 'the findings of HERS should not discourage the use of hormone replacement therapy in the primary prevention of cardiovascular disease'.

Grodstein's recent study was commented on in an Editorial [4] by Grady and Hulley who question, 'When are observational studies adequate evidence?'. They are the leading authors of the much publicised HERS Study [5].

Grady and Hulley seem to overlook a number of pitfalls of their HERS Study, some of which were mentioned in my letter to the editor of Climacteric [6].

The HERS Study, as interpreted by a practitioner, is nothing but a *phase III Study* of a *particular* product (0.625 mg of conjugated equine estrogens plus 2.5 mg of medroxyprogesterone acetate, in one tablet daily) It is *not* a study of estrogen/progestin replacement in postmenopausal women. The protocol of the study *does not* reflect good clinical practice. It is not conceivable that older women ('participants range in age from 44 to 79 years') are kept on a treatment that is obviously excessive, as pointed out by Hulley et al. ('persistent vaginal bleeding occurred in 34 women; 30 in the hormone group, among whom one primary CHD event occurred')!

They acknowledge that, 'breast discomfort and vaginal bleeding were reported directly to the

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PII: S0378-5122(01)00181-5

gynaecology staff,' although they do not mention either how many women had these complaints, or if the recorded cardiovascular events had a higher incidence in that group, or the reasons for a 20% drop out.

Their study group was really very sick: 'established coronary disease was defined as evidence of one or more of the following: coronary artery bypass graft surgery, percutaneous coronary revascularization, or angiographic evidence of at least a 50% occlusion of one or more major coronary arteries'!

Despite these facts, primary CHD occurred only in 172 of the 1380 women in the hormone group and in 176 of the 1383 women in the placebo group. This is four cases less in 1380 women! In other words, the hormone group had an incidence of 12.46% and the placebo group had 0.26% lesser occurrence of primary events. 'The RH comparing risk of the primary CHD outcome in the hormone and placebo group was similar', they say. The CHD deaths were 5.14% for the hormone treated group and 4.19% for the placebo group, that is less than one more death in 100 treated women!

The same AA also conclude that, 'Total mortality in the hormone group was not significantly different from that in the placebo group (131 vs. 123 women)'.

For a practitioner these figures are far from being impressive in the light of other secondary and primary prevention trials. As Hulley et al. conclude 'The discrepancy between the finding of HERS and the observational studies may also reflect important differences between the study populations and treatments'. 'The higher rate (thrombotic events) is probably a consequence of the facts that women involved in HERS were older and had multiple risk factors'.

It is also not necessarily correct to plot the data in woman/years since this calculation does not take into account the duration of treatment preceeding an event.

It seems that much of what is said about the HERS study and what is written in the Editorial by Grady and Hulley is not clinically relevant since they state [4] that the, 'HERS did not evaluate the effect of estrogens plus progestin therapy in women without CHD, and it is not known whether our findings apply to healthy women. It is also not known whether the use of different progestin or of estrogens alone would have been beneficial'.

Is it not very strange that [5], 'For women who stopped taking HERS medication, risk of primary CHD events was elevated in the first month after stopping use of the medication'?!

I have difficulty in understanding why Grady and Hulley [4] admit that, 'Perhaps postmenopausal hormone therapy is beneficial in women who have not yet developed coronary disease but not in women who already have it,' and conclude their remarks saying that they, 'believe that the disappointing results of three recent trials indicate that clinicians should not use hormone therapy for prevention of coronary disease until this practice is supported by evidence from randomised trials'!

The conclusion of Grodstein et al.'s report has great clinical importance. 'The Nurse's Health Study investigation of primary prevention indicates that hormone therapy may be associated with coronary benefits'.

The higher the risk for cardiovascular disease in a population the greater is the HRT preventive effect. In a study of dutch [7] women it was concluded that HRT started at age 55 for 10 years can prolong life and that, 'one excess breast cancer case is likely to occur per 5–6 averted cases of first myocardial infarction or hip fracture'. 'For a woman with high-risk profile, the gains in health are about twice as high as for her counterpart in the general population, and her risk–benefit ratio is also more favourable'.

So, what?

Is the *Queen* really naked?

Yes. I think so.

Every discussion about the Menopause (*the Queen*...) seems to implicate that there is nothing but HRT!

First of all, there are many different postmenopausal hormone therapies: different estrogens, different progestins, different routes of administration, different regimens, which have different profiles [8,9].

Second, there are those who know and those who do not know how to tailor-make it to a particular woman and to monitor its efficacy in the targets that have justified its selection.

Third, there are those who think that the menopause is a disease to be treated solely with sex hormones, and there are those who believe that the menopause is an event in a middle-aged woman's life.

Under these circumstances the time has come, for those who take care of menopausal women, to realise that there are also many other very important and effective strategies to prevent cardiovascular diseases.

Lori Mosca et al. have published [10] a, 'Guide to Preventive Cardiology for women'. This is a very important document to be studied and used. It appears that half of the benefits in the prevention of cardiovascular diseases are not hormone related!

Last October, the International Menopause Society had organised an, 'Expert Workshop' on 'Cardiovascular Disease and Hormone Replacement Therapy' which took place in London, at the Royal Society of Medicine [11]. It was concluded that. 'all medical interventions should be individualised to the specific woman's age, characteristics and needs. The ultimate effects of different dosages, schedules and type of hormones used should be clarified, avoiding inferring the effects of one form of HRT to others. The importance of increased attention to life-style factors such as healthy diet, exercise and cessation of smoking should be underlined since these can confer specific benefits also to menopausal women'.

The important issue, after all, is not HRT. What is important is the best possible approach to preventive medicine in a middle-aged woman.

However, at the present time, HRT seems to be the best pharmacological available strategy to improve brain function and to prevent colon cancer.

Those who only investigate HRT and never see a patient may have doubts about the enormous benefits of HRT in terms of quality of life. How many women must be on HRT to prevent one cardiovascular event at the expense of how many more (?) *diagnosed* breast cancers is something that is too far away from a woman's mind when she feels that more life has been added to her years.

And, after all, only 20% of women who start HRT seem to continue treatment after 4 years [12]…

So, what?...

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