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Treatment of the menopause: the swinging pendulum

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Introduction

Facts and views on the treatment of the menopause underwent dramatic swings during the last fifty years, from a non-issue fifty years ago to a must for the well-being of all postmenopausal women at the end of the 20th century. The enthusiasm for hormone replacement therapy (HRT) was smashed in 2002, after the publication of a large-scale prospective randomised study, the WHI trial, on health costs and benefits of hormonal therapy of postmenopausal women (Writing Group for the Women's Health Initiative Investigators, 2002). This study concluded that on balance the side effects of hormonal treatment of the menopause outweigh the potential benefits. The undue and mostly uncritical attention to this publication in the media alienated a great deal of doctors and patients from a treatment that hitherto was deemed to be a boon for the postmenopausal woman. Several editorials in leading medical journals cautioned against the use of hormone replacement therapy and they expressed stern criticism of the naïve belief of gynaecologists in the prophylactic benefits of HRT (Herrington and Howard, 2003; Sackett, 2002; Lagro-Janssen, 2003). It was only after years of debate between advocates and opponents of HRT and detailed additional analysis of the WHI trial that HRT could be put into its proper perspective. Not only is HRT the most effective treatment of cumbersome menopausal symptoms that can be administered safely to all healthy women for a limited period of time, but the prophylactic properties of HRT with regard to cardiovascular disease and osteoporosis can and should be taken advantage of in appropriate cases.

We aim to briefly outline the history of HRT and to propose what currently can be considered as reasonable guidelines for the treatment of postmenopausal women.

The rise of HRT

The start for a systematic hormone therapy of all postmenopausal woman was given in the U.S by dr. Robert A Wilson who promoted this therapy in his book 'Feminine Forever' (1969). He was the first to consider the menopause as a disease which should be treated in a proper way *'Many physicians simply refuse to recognize menopause for what it is — a serious, painful and often crippling disease. Every woman alive today has the option of remaining feminine forever.'* The term hormone replacement therapy was hitherto reserved for young women who went either spontaneously or artificially into premature menopause. The proselytizing endeavour of dr. Wilson in the U.S. led to the large-scale use of Premarin® which contained estrogens extracted from pregnant mare urine. This first wave of enthusiasm, mostly limited to the U.S., was temporarily tempered when observational studies indicated that long-term administration of unopposed estrogens increased the risk for endometrial carcinoma sevenfold (Ziel and Finkle, 1975). When it became clear that this risk could be countered by the addition of progestagens either in a sequential or continuous fashion, several formulas of oestro-progestagen combinations were marketed. The

rationale for HRT was further supported by several observational studies which indicated that HRT, besides its beneficial effects on menopausal symptoms, also could have a role in the prevention of osteoporosis and cardiovascular disease. The most notable among them was The Nurses' Health Study (Grodstein *et* al., 1996). This was a prospective observational study involving 121.700 nurses of 30 to 55 years old, the results of which indicated that the risk of cardiovascular disease was significantly less in women taking HRT. A later analysis also revealed that the risk of lethal disease was also significantly lower in HRT users, particularly for women with existing coronary risk factors (RR 0.63) (Grodstein *et al*., 1997). With this preliminary evidence of the beneficial effects of HRT for postmenopausal women a potential mass consumption could be anticipated. Numerous new hormone preparations were developed and actively promoted by pharmaceutical companies. The dream of Wilson was on the verge of coming true.

The reverse swing of the pendulum

The swing of the pendulum went into reverse in the beginning of the 21st century in the wake of the publication of two prospective randomized studies on the effect of HRT. The starting point of both studies was to prove or refute the alleged beneficial effects of the systematic administration of HRT to postmenopausal women. The first study (the HERS trial) was intended to investigate the cardiovascular effects of HRT in women with coronary risk factors (Hulley *et al*., 1998). When the results were published in August 1998 it was clear that in contrast with the Nurses' Health study (Grodstein *et al*., 1997), HRT had no place in the prevention of cardiovascular disease, at least in cardiovascularly compromised women. The final blow, however, was given by the publication of the results of a large prospective randomized trial on the effect of HRT in healthy postmenopausal women, the 'Women Health Initiative Trial'. In the first arm of this study 16.608 healthy postmenopausal women with an intact uterus were randomised for a treatment with conjugated oestrogens (Premarin®, 0.625 mg) combined with medroxyprogesteronacetaat, 2.5 mg per day or placebo. The second arm comprised 10.789 healthy women without uterus which were randomised for a treatment with Premarin® 0.625 mg per day. The first arm, which was meant to last 8,5 years was discontinued after 5 years because an interim analysis showed that the balance of beneficial and adverse effects was negative. The three main adverse effects were an increased risk for deep vein thrombosis, breast cancer and cardiovascular events. The relative and absolute risks for beneficial and adverse effects are given in Table 1 en 2. The general conclusion of the authors of the WHI trial was that long-term HRT is associated with more adverse than beneficial effects. This publication got extensive coverage in the media worldwide and unleashed a torrent of comments in leading medical journals. The editorial of the Lancet of 9 August 2003 was very explicit: '*The new evidence of breast cancer mortality dictates an explicit position: HRT should be discouraged and practitioners should seek alternative solutions*' (Lagro-Janssen *et al*., 2003). Another editorial read like an outright diatribe against gynaecologists and pharmaceutical companies alike (3). In this editorial

Table 1. — Relative risks and benefits of combined HRT according to the WHI trial

	Relative risks	Confidence Intervals
Coronary incidents	1.29	1.02 – 1.63
Breast cancer	1.26	1.00 – 1.59
CVA	1.41	0.86 – 2.31
DVT	2.11	1.26 – 3.55
Endometrial cancer	0.83	0.29 – 2.32
Colorectal cancer	0.63	0.32 – 1.24
Hip fractures	0.66	0.33 – 1.33
Vertebral fractures	0.66	0.32 – 1.34

Table 2 — Absolute risks and benefits of combined HRT according to the WHI trial. Incidence of events expressed per 10.000 woman years

	HRT	Placebo	
Coronary incidents	37	30	+7
Breast cancer	38	30	+8
CVA	29	21	+8
DVT	34	16	+18
Endometrial cancer	5	6	-1
Colorectal cancer	10	16	-6
Hip fractures	10	15	-5
Vertebral fractures	9	15	-6

Prof. D. L. Sackett wrote: '*There is a need for a higher standard of evidence before an agent is advocated solely for disease prevention. The blame is to be set on the shoulders of medical experts who advocated 'preventive' manoeuvres that have never been validated in rigorous randomized trials to: gain profit from industry affiliation, to satisfy a narcissistic need for public acclaim or in a misguided attempt to do good.*' (Sackett, 2002). Although this statement held some truth, it risked to throw away the baby with the bathwater. Indeed, the first conclusion of the WHI was that the risks for breast cancer and cardiovascular disease do not outweigh the benefits of HRT for the treatment of menopausal symptoms in young women (< 56 years). Unfortunately, in all the criticisms of HRT, this statement was, deliberately or not, overlooked. Moreover, the results of the WHI trial are only applicable to the population studied and should not be indiscriminately applied to all postmenopausal women. Nevertheless, the consumption of HRT dropped worldwide with 50%.

Return of the pendulum?

One of the criticisms of the WHI trial was that the mean age of the participants was 63 yrs and that 36% of the women had a BMI > 30. This certainly is not the profile of European women starting HRT. The majority of them start HRT at the time of the menopause, i.e. at a mean age of 52 and most of them will have stopped HRT by the age of 62. In later analyses of the WHI data, it appeared that timing of HRT determines the cardiovascular risk. Grodstein et al (2006) reported a statistically significant trend of coronary heart disease events with time since menopause in the WHI study. Rossouw *et al*. (2007) reported that women who initiated therapy closer to menopause tended to have reduced coronary heart disease risk compared with the increase in coronary heart disease risk among women more distant from menopause. On the other hand, there is evidence that the risk for breast cancer is higher when HRT is started closer to the menopause (Prentice *et al*., 2009)

In 2004, the results of the second arm of the WHI trial involving 10.789 women which were treated with oestrogen alone were published (The Women's Health Initiative Steering Committee, 2004). No increased risk of breast cancer was observed in this group, confirming that the risk of breast cancer is mainly due to the combined oestrogen-progestin treatment. It is doubtful, however, that this effect can be generalized to all progestins. Indeed, there is some evidence that natural progesterone or related progestins have no deleterious effect on breast tissue (Fournier et al., 2005).

Recommendations for hormonal therapy of the menopause anno 2010

The role of hormonal replacement therapy has been put on the wrong track by its own name, which in fact is a misnomer. In contrast with replacement therapy when other endocrine systems fail (thyroid, adrenal…) oestrogens have no vital role after the menopause. The biological function of oestrogens, including its effect on the cardiovascular system and the bones, is limited to the reproductive years. This does not mean, however, that oestrogens have no role in the treatment of menopausal women. In fact, they are the best option for treating menopausal discomfort and their effect on the vascular system and the bone can be advantageous for some postmenopausal women. Therefore, the term hormonal therapy of the menopause is to be preferred to the term hormone replacement therapy.

Considering all available evidence some guidelines concerning hormonal therapy of the menopause can be proposed.

Oestrogens can safely be given for five years to perimenopausal women suffering from hot flushes. This is also in accordance with the statement of the authors of the WHI Study.

A continuous or cyclic association with progestins is necessary for women with a uterus in place. In hysterectomized women a treatment should consist of oestrogens alone.

Oral oestrogens increase the risk for thrombosis and should not be prescribed to susceptible women.

Both systemic and vaginal oestrogens are effective in case of vaginal atrophy but vaginal oestrogen is the preferred therapy for isolated vaginal symptoms.

Risks and benefits should be balanced in women taking HRT for more than 5 yrs.

Although oestrogens are not indicated for the prevention or treatment of osteoporosis their beneficial effect on bone turn over can be taken into account when other indications for HRT are present.

Although the risk of breast cancer is small, women should be informed that this risk becomes significant after 5 yrs of treatment. It seems that oestrogens, particularly in association with progestins do not induce breast cancer but enhance the growth of incipient cancers causing more breast cancers to be detected after long term treatment. This hypothesis is substantiated by the fact that there is no difference in mortality between women who do and do not take HRT.

In contrast with the findings of observational studies, oestrogens have no role in the prevention of cardiovascular disease but it seems that HRT when started early in the menopause does not increase the risk and even may have a protective effect.

It seems logical to treat women with premature menopause with HRT until the age of natural menopause; i.e. approximately 52 yrs. Although there is no hard evidence for the beneficial effect, it should be kept in mind that women with untreated premature menopause have an increased risk of cardiovascular disease (Rosenberg *et al*., 1981).

Conclusion

Premature conclusions from the WHI study, which were largely overstated by the mass media have led to a negative appraisal of the beneficial role of HRT. The first conclusion of the WHI study, however, stated that the balance of risks and benefits of HRT in symptomatic women in early menopause is positive. Reanalyses of both the WHI study and the observational studies have shown that there is in fact less contradiction between observational studies and randomised trials but that differences are mainly due to the timing of HRT therapy (Phillips and Langer, 2005). Considering all data now available, hormonal treatment of the menopause has now become full circle. In contrast with the policy of ten years ago, menopausal symptoms and not prevention of whatever potential disease is the main indication for treatment. It can safely be given to all symptomatic women during the perimenopause or shortly after the menopause. If symptoms warrant further treatment after 5 years, a small increase in the risk of breast cancer should be taken into account and discussed with the patient.

References

Fournier A, Berrino F, Riboli E *et al*. Breast cancer risk in relation to different types of hormone replacement therapy in the E3 N-EPIC cohort. Int J Cancer. 2005;114:448-54.

Grodstein F, Stampfer MJ, Manson JE *et al*. Postmenopausal estrogen and progestin use and the risk of cardiovascular disease. N Engl J Med. 1996;335:453-61.

Grodstein F, Stampfer MJ, Colditz GA *et al*. Postmenopausal hormone therapy and mortality. N Engl J Med. 1997;336: 1769-75.

Grodstein F, Manson JE, Stampfer MJ. Hormone therapy and coronary heart disease: the role of time since menopause and age at hormone initiation. J Womens Health (Larchmt). 2006; 15(1):35-44.

Herrington DM, Howard TD. From presumed benefit to potential harm—hormone therapy and heart disease. N Engl J Med. 2003;349(6):519-21.

Hulley S, Grady D, Bush T *et al*. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. Heart and Estrogen/progestin Replacement Study (HERS) Research Group. JAMA. 1998; 280(7):605-13.

Lagro-Janssen T, Rosser WW, van Weel C. Breast cancer and hormone-replacement therapy: up to general practice to pick up the pieces. Lancet. 2003;362(9382):414-5.

Phillips LS, Langer RD. Postmenopausal hormone therapy: Critical reappraisal and a unified hypothesis. Fertility and Sterility. 2005;83:558-66.

Prentice RL, Manson JE, Langer RD et al. Benefits and risks of postmenopausal therapy when it is initiated soon after menopause. Am J Epidemiol. 2009;170:12-3.

Rosenberg I, Hennekens CH, Rosner B *et al*. Early menopause and the risk of myocardial infarction. Am J Obstet Gynecol. 1981;139:47-51.

Rossouw JE, Prentice RL, Manson JE *et al*. Wu L, Barad D, Barnabei VM, Ko M, LaCroix AZ, Margolis KL, Stefanick ML. Postmenopausal hormone therapy and risk of cardiovascular disease by age and years since menopause. JAMA. 2007;297(13):1465-77.

Sackett DL. The arrogance of preventive medicine. Can Med Assoc J. 2002;167:363-4.

The Women's Health Initiative Steering Committee. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy. The Women's Health Initiative Randomized Controlled Trial. JAMA. 2004;291,1701-12.

Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. JAMA. 2002; 288:321-33.

Ziel HK, Finkle WD. Increased risk of endometrial carcinoma among users of conjugated estrogens. N Engl J Med. 1975; 293:1167-70.