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Continued Overleaf

## Postmenopausal hormone replacement therapy

*We need to clarify our practice guidelines and open a dialogue with our patients*

One of the most difficult health care decisions that women and their doctors have to make today concerns postmenopausal hormone replacement therapy (HRT) [1]. Menopause, defined as the cessation of periods for 6 months or more, is just one event during the natural biological process of ovarian atrophy that begins as early as the mid-thirties. It is accompanied by varying degrees of short term symptoms such as hot flushes, night sweats, mood swings and insomnia, to long term problems that determine frailty, durability and death of women, viz., urogenital atrophy, osteoporosis, coronary artery disease, stroke and cancer. Most of these changes are attributed to ovarian deficiency, so it makes sense to replace deficient hormones to sustain premenopausal youth and quality of life, to satisfy the eternal human desire for good health and immortality [2].

Currently, an average woman lives more than a third of her life after the menopause. This is also the phase in her life when the risk of cardiovascular disease, cancer, osteoporosis and cognitive decline are highest. Although women live longer than men, they are reported to have a poorer health related quality of life [3]. Does HRT eradicate or attenuate these problems? Usually HRT is (or means) treatment with oestrogen alone or oestrogen in combination with progesterone. HRT nearly doubles the circulating hormonal concentration in a postmenopausal woman, without reaching that of a premenopausal woman [2]. Data from a national survey in the USA in 1997 revealed that 45% of women born between 1897 and 1950 took HRT at least for 1 month and 20% continued for 5 years or more [4]. In Britain HRT was used by about one third of women aged 50 to 64 years [5].

In the 1950s there was little interest in HRT, although by the 1960s it was regarded as the "fountain of youth" for postmenopausal women. In the 1970s there was concern about the risk of endometrial cancer developing in women with an intact uterus taking oestrogen alone. Since combination HRT appeared to reduce uterine cancer risk and osteoporotic fractures, the 1980s saw the emergence of "HRT evangelists" who believed that HRT must be given to every postmenopausal woman [6]. But where was the evidence? Were all the risks reliably quantified? Long term health benefit of HRT was based on retrospective, observational and case control studies, without strong supportive evidence from prospective, randomised, placebo controlled clinical trials.

The 1990s saw some concern raised about increased breast cancer, particularly with combination HRT [7], that was further substantiated by the Million Women's Study in the UK [8]. The HERS trial further swung the course of the HRT pendulum by showing a rise in coronary artery disease

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(CAD) soon after initiating HRT for secondary prevention of CAD [9]. Medical practitioners formed treatment biases based on clinical priorities of specific groups of their patients, a phenomenon called the Bayesian prior probability bias. For example, a gynaecologist attending on predominantly premenopausal young healthy women with disabling perimenopausal symptoms has an impression of the place of HRT specific to such a group, whereas a geriatrician attending on elderly women with established cardiac disease holds a different view [6]. With respect to cardioprotective effect of HRT, although gynaecologists promoted HRT for primary prevention of CAD and not its secondary prevention, non-gynaecologists suggested HRT for secondary prevention of CAD. The HERS trial tested prospectively the effect of HRT in women with established heart disease who also had an intact uterus. HERS showed a rise in CAD adverse events in the first year of the study, which reduced over the third to fifth year of HRT [9].

The National Institute of Health (NIH) dropped a bombshell when it terminated prematurely in 2002 the Women's Health Initiative (WHI) study, because the adverse effects of combined HRT outweighed its benefits [10]. The oestrogen alone arm of the WHI study was expected to re-assess the true place of combination therapy by 2005. Nevertheless, it was also prematurely terminated in April 2004 due to the lack of substantial evidence that oestrogen reduces the risk of CAD [11]. Hence, it is appropriate that our medical community takes stock of the current status of postmenopausal HRT based on hard evidence, and reconsider its use in our practice based on clear and rational guidelines.

### What do we tell our patients now?

Designed as the first prospective, statistically powered, randomised controlled clinical trial on postmenopausal women, the WHI is impressive and unlikely to be challenged by future studies [6]. Two parallel trials were undertaken from 40 centres in the USA with a follow up period of 8.5 years, of ethnically diverse healthy women aged 50 to 79. The primary outcome measures were incidence of a CAD related event, stroke, pulmonary embolism, invasive breast cancer, hip fracture, colorectal cancer and death due to other causes. One arm comprising 16 608 women to assess the use of conjugated equine oestrogen (CEE), 0.625 µg, in combination with medroxyprogesterone acetate (MPA), 2.5 mg, was terminated early at 5.2 years, since the global index for harmful outcomes (coronary events, stroke, breast cancer and pulmonary embolism) outweighed the benefits (reduced risk of hip fracture and colon cancer) [10]. The other arm with 10 739 healthy women with hysterectomy assigned to test CEE alone was terminated early at 6.8 years because of the increased risk of stroke and no reduced risk of CAD, although with reduced hip fracture [11]. Limitations of WHI include the testing of a single oestrogen preparation and MPA, at a single dose administered orally, and a relatively short follow up period. The impact of WHI results that were publicised in the medical and lay press led to dramatic negative reactions among doctors and patients with significant HRT discontinuation rates in the USA [12].

In real terms what did WHI demonstrate? Among 10 000 women treated for one year with combined HRT, the numbers affected by diseases in excess of a control group not taking HRT would be: seven more CAD related events, eight more strokes, eight more pulmonary embolisms, and eight more invasive breast cancers; while six less colorectal cancers and five less hip fractures would occur in those taking HRT. Seemingly low on an individual basis, taken collectively the hazard ratio for disease and death from HRT was unacceptably high to recommend long term use as a disease preventing drug. The WHI results have far reaching implications, although questions arose whether MPA alone was the villain. The impact of HRT on quality of life

was not assessed, and the average age of participants was mid-60s. Although the CEE alone arm took longer to show lack of clear benefit to prevent CAD and stroke, which may be due to less statistical power (only 10 000 women), it clearly excluded MPA being the problem [6, 13].

In summary, HERS and both arms of WHI trials clear previous misconceptions of HRT being cardioprotective and demonstrate an increased risk of stroke and pulmonary embolism. The cancer risks with HRT showed a clear trend towards an increased risk of breast cancer (particularly with progesterone), whereas combined HRT is protective for colorectal cancer. HRT is clearly beneficial in reducing hip fracture [6, 10,11,13]. The rise of hazard risks of HRT with age, and the fact that younger women (in their 50s) experience disabling symptoms of menopause, favour safe treatment of symptoms associated with menopause using HRT for the shortest possible time, where possible with oestrogen alone, in the lowest effective dose. However, to prevent chronic disease, there is no evidence of an overall benefit by oestrogen alone. Combination therapy is harmful, and HRT in its current form and dose should not be advocated for long term use.

On a practical note, we need to open a dialogue with our patients where the individual woman shares in decision making about commencing HRT. It is essential to counsel about the exact meaning of "increased risks of HRT", but the emphasis on the appropriate diet and lifestyle changes to preserve general health and well being must not be forgotten. Those who opt to take HRT need to be advised to limit it for a maximum of five years, during which an annual mammogram and health check are mandatory. Combined HRT is not indicated for women without symptoms. Asymptomatic women already taking HRT must re-consider the decision. Alternatives to HRT, such as the selective oestrogen receptor modulators (eg. raloxifene hydrochloride), must be considered for long term use.

A recent editorial warns doctors against playing up the disease risks reduced by HRT while down-playing the hazard risks of HRT, especially by citing results of subgroup analyses, which could pave the way to irresponsible marketing [14]. Women also need to be cautioned against alternative and complementary medications that have insufficient safety data. Further clinical trials with clear primary end points are necessary before using alternative formulations and modes of delivery of long term HRT. Until then we need to clarify our own practice guidelines.

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