Menopause and hormone therapy – how confused are you?

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Where hormone therapy in the menopause is concerned a line was drawn on 9 July 2002 between two eras: the pre- and post-Women's Health Initiative study.[1] On this day the combined oestrogen-progestogen arm of the largest randomised controlled trial (RCT) was discontinued prematurely at just past 5 years. Unusually, the lay media reported on it before it was published and doctors were caught on the back foot when irate patients started calling their rooms to find out about their increased breast cancer, heart attack, stroke and pulmonary emboli risk that they had read about.

The primary aim of the WHI RCT study was to test the effects of hormone therapy on postmenopausal women's risk for coronary heart disease, breast cancer and hip and other fractures. The study was launched in 1991 and included 10 735 women in the oestrogen-only arm and 16 608 women in the oestrogen-plus-progestogen arm. The age range of the women in the study was 51 - 79 (16 608 women), with an average age (63.3) at least 12 years later than the average woman would normally have presented with menopausal symptoms and need or request hormone therapy.

In the words of Jacques Rossouw, principal investigator of the WHI study: 'The Women's Health Initiative study results tell us that during one year, among 10 000 postmenopausal women with a uterus (as opposed to those who have had the uterus removed) who are taking oestrogen plus progestogen, 8 more will have invasive breast cancer, 7 more will have a heart attack, 8 more will have a stroke, and 18 more will have blood clot in the lungs and legs, than will a similar group of 10 000 women not taking these hormones. This is a relatively small annual increase in risk for an individual woman.' The study did, however, show a reduction in colon cancer and hip fracture risk in the oestrogen-plus-progestogen arm.

Up until 2002 almost reflex scripting of hormone replacement therapy for menopausal women was common among doctors, irrespective of whether a woman was symptomatic or not, and therein lies part of the reason for the patient backlash against the allopathic approach to management of the menopause. Prior to the WHI study we assured women that, in addition to symptomatic relief and prevention of osteoporosis, a small increase in breast cancer was offset by the 50% reduction in heart disease risk shown in observational and epidemiological studies.[2] We were now being accused of possibly being instrumental in causing cardiovascular deaths.

Cardiovascular disease

The *age of initiation of hormonal therapy* has given rise to the concept of a window of cardiac opportunity around the time of the menopause, thus giving credence to the earlier observational and epidemiological studies.

Some of the many roles of oestrogen before that final menstrual period include keeping arterial walls free of atherosclerosis by maintaining a favourable lipid profile, ensuring vascular wall relaxation and dilatation and preventing insulin resistance, which are all cardio-protective functions. The menopause heralds a dramatic reduction in oestrogen production with a concomitant increase in cholesterol deposits in arterial walls with trapping of cells which become calcified. Thickening of the arterial walls and associated calcified plaques contribute to the development of atherosclerosis as we age and the assumption is that the increased cardiovascular events seen in the WHI represent hormone-induced effects on unstable plaques. Exogenous hormone therapy is considered to stimulate arterial inflammation with subsequent plaque rupture, clot formation around dislodged particles which can block vessels, resulting in myocardial attack or stroke. The Heart and Estrogen/progestin Replacement Study (HERS) Research Group (I and later II) studies in women who had known pre-existing cardiovascular disease initially raised questions about the increase in heart attacks in the first year of hormone therapy use, but it was the publication of the WHI few years later that raised the alarm.[3]

Venous thromboembolism remains a risk, especially in smokers, women with previous deep vein thrombosis and/or pulmonary emboli. The transdermal route of administration may be important in decreasing this risk in selected women. Bypassing entero-hepatic circulation by using 17-beta-oestradiol on its own or with progesterone in women with uteri is recommended for this at-risk group.[4]

Breast cancer

Women generally fear breast cancer more than they do cardiovascular disease and could simply not *hear* that only one arm on the study had been discontinued (oestrogen-progestogen therapy) and that women with hysterectomies (oestrogen therapy), by default, were at a distinct advantage where breast cancer and cardiovascular disease were concerned.

Certain oestrogen-progestogen hormonal therapy combinations are associated with an increase in breast cancer. It may, however, be dependent on whether it is given as a continuous combination versus a sequential regimen, how long it is given, at what dose and how it is administered, as well as which progestogens are used. Medroxyprogesterone acetate has been maligned since WHI, but norethisterone acetate has been implicated with a higher risk of breast cancer. Recent Finnish data negate the general consensus that oestrogen alone does not increase the risk of breast cancer, neither does the addition of testosterone to oestrogen therapy.[5]

Recent studies support the notion that hormonal therapy promotes pre-existing lesions which are generally detected early, run a less sinister course and do not result in an increased mortality rate due to breast cancer when compared with non-users of hormone therapy. It is also reassuring that risk returns to that of the background population within a few years of stopping hormone therapy and that the risk increase with oestrogen-progestogen therapy does not occur before 3 - 5 years of use.

Osteoporosis

Results of the WHI showed that the use of conjugated equine oestrogen (CEE, 0.625 mg daily) together with medroxyprogesterone acetate (MPA, 2.5 mg daily) reduced the risk of hip and

clinical vertebral fractures by 34%, and the overall risk of fractures by 24%, compared with placebo. (These percentages are calculated from the associated hazard ratios reported in the study.) This risk reduction amounted to 5 fewer hip fractures per 10 000 women per year.

Where are we going to?

Since 2002 newer, lower-dose hormone therapy preparations, both oral and transdermal, have come into the market and are starting to find their niche. Parallels may be drawn with the evolution of the now safe, efficacious and mainly metabolically neutral low-dose oral contraceptive pills which now have the added advantage of significantly decreasing the risk of both endometrial and ovarian cancer and can be used quite safely in smokers up to the age of 35.

All controversies spawn new approaches and we will soon be able to use non-hormonal therapy for vasomotor symptoms. Neuroleptic agents and selective serotonin and seratonin-norepinephrine re-uptake inhibitors are already being used extensively in women who choose not to use hormone therapy or have a contraindication for the use thereof.

Position statements abound globally and are under constant review. The South African Menopause Society published its revised statement on menopausal hormone therapy in 2007.[6]

The principles of the lowest effective dose for the shortest necessary duration rule.

According to the South African Menopause Society guidelines, oestrogen therapy does not increase the risk of breast cancer, but increases the risk of endometrial cancer in non-hysterectomised women.

Indications for hormone treatment

- Treatment of vasomotor symptoms and associated sleep disorders.
- Treatment of symptomatic urogenital atrophy.
- Prevention of bone loss in women aged between 50 and 60 who are at the risk of fracture, with or without vasomotor symptoms, while recognising that there are other proven non-hormonal modalities of treatment for osteoporosis.

It is generally accepted that women with premature ovarian failure should be offered hormone therapy until at least the average age of expected menopause, which is considered to be 51 years.

Previously hormonal therapy was also hailed as having such a beneficial effect on cognitive function, that Alzheimer's disease progression could be retarded. Hormone therapy, however, is not indicated for the treatment of Alzheimer's disease.

Contraindications to hormone therapy

- Current, present or suspected breast cancer.
- Known suspected oestrogen-dependent tumours.
- Undiagnosed genital bleeding.
- Untreated endometrial hyperplasia.
- Previous idiopathic or current venous thromboembolism.
- Known arterial coronary heart disease.
- Active liver disease.
- Porphyria cutanea tarda is an absolute contraindication.

Profiling women

By now it must be abundantly obvious that the 'one size fits all' approach of the past can no longer continue. Indications, dose, duration of treatment, current and future co-morbidities should all be considered prior to initiation and reviewed on at least an annual basis.

Initiation of hormone therapy in women over the age of 60 years should be avoided. Prerequisites prior to initiation of therapy include a full general, systemic and gynaecological examination which ideally includes a pelvic ultrasound examination to exclude pre-existing gynaecological pathology, a baseline mammogram and a fasting glucose level and lipogram.

Bone mineral density assessments depend on the patient profile and whether she chooses to use hormone therapy or not. Recognising the development of insulin resistance and being on the look-out for thyroid dysfunction all form part of a menopausal risk assessment.

Given the metabolic and mental impact of a dwindling ovarian reserve, the peri-menopause and menopause present an ideal opportunity to intervene on multiple levels to ensure increased longevity and quality of life of women in a comprehensive manner.

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