



THE CEYLON MEDICAL JOURNAL

Established 1887

The Official Publication of the
Sri Lanka Medical Association
Volume 60, No.2, June 2015
Quarterly ISSN 0009-0875

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Caring for women in their post reproductive life: current recommendations on hormone replacement therapy

Introduction

The post reproductive life denotes the period in a woman's life after she reaches menopause and is a period that brings about many physical as well as psychological changes. Menopause is a diagnosis usually made in retrospect by the absence of menstruation for more than one year. However, ovarian function is known to diminish by late 30s, resulting in complete failure by the early 50s in most women [1]. This period of change in ovarian function is called the menopausal transition. A woman may experience many symptoms during this transition and in the postmenopausal age that ensues.

The main symptoms of menopause include vasomotor symptoms, problems related to changes in urogenital epithelium and those due to impaired cognitive functions. The sexual function of women is also affected due to these effects as well as other changes. As the average life expectancy of a woman in Sri Lanka is 79 years and the mean age of menopause is around 51 years nearly one third of a woman's life will be post menapausal [2].

New challenges in post-reproductive age

Women contribute significantly to the present day work force and many hold key positions by the time they reach menopause. Therefore the general wellbeing during this transition is important. Furthermore, women are becoming more and more socially active and engage in many physical activities and travelling, thus exposing themselves to risk of accidents and injuries. In societies such as Sri Lanka even older women who are not engaged in occupations remain active within their extended families, caring for grandchildren. All these demand a great deal of physical as well as psychological wellbeing.

The increased life expectancy has increased the number of women in the post reproductive age who have non-communicable diseases. Therefore, prevention of disease was declared the main focus of the International Menopause Day in 2014 by the International Menopause Society [3].

Obesity is an emerging problem worldwide affecting health of many. Obesity increases the risk of certain conditions in women after menopause. These include higher risks of malignancies such as endometrial cancer, coronary heart disease, diabetes mellitus and thrombosis. These risks have to be considered when deciding on use of HRT.

Rapid changes in evidence regarding the benefits and risks of hormone replacement therapy (HRT) is challenge to the clinicians as well as patients

[4]. Because of conflicting messages in the popular press, women find it difficult to understand the associated risks and benefits of HRT. Providing adequate evidence so that women can make informed decisions regarding HRT has become a challenge [5].

Health problems in the post-reproductive age

In menopause there is not only reduction of oestrogen production from the ovaries, but many hormone systems in the body are also affected [6]. Oestrogen deficiency results in symptoms such as hot flushes, sweating, insomnia, vaginal dryness and discomfort [1]. Such symptoms can affect up to 85% of women. While symptoms tend to cease within five years in most, they can persist beyond that in a significant proportion [1].

In the menopause transition and postmenopausal age group there can be impairment of memory and other cognitive functions [7]. Evidence suggests that it is most pronounced during the transition, improving later in the post menopausal period [7].

Reduced levels of oestrogen affect bone metabolism resulting in reduced bone mineral density which, over time when left unrecognised, can develop into osteoporosis [8]. Some studies report prevalence of osteoporosis as high as 70% by the age of 80 years [9].

Sexual dysfunction in women during the post-reproductive age is often a neglected area, especially in Asian cultures. However, with improvement in general living conditions women are now more concerned about sexual wellbeing in later life [10].

Women seek medical help due to menopausal transition and associated symptoms. This should be used as an opportunity to carry out a risk assessment and take appropriate measures that will not only increase their life span but also improve quality of life [3].

The current status of HRT

The benefits and risks of HRT has been debated much. The British Menopause Society (BMS) and Women's Health Concern have made recommendations on HRT [11]. These are similar to the 2013 updated guidelines of the International Menopause Society (IMS), an umbrella organisation of many menopause societies around the world, and the North American Menopause Society [12,13]. These reflect the current understanding of benefits and risks of HRT. The key recommendations on HRT are as follows:

- Oestrogen remains the most effective treatment for relieving vasomotor symptoms. Long-term use of HRT may improve mood and depressive symptoms. Vaginal symptoms and sexual dysfunction can be treated with either systemic or topical use of HRT. This can improve bladder symptoms such as frequency and urgency through beneficial effects on the bladder

and urethral epithelium. When topical oestrogens are used in small doses, there is no need for the addition of progesterone.

- Though the protective effect of HRT on osteoporosis is proven, currently regulatory authorities do not recommend use of HRT for the sole purpose of preventing osteoporosis as risks outweigh the benefits. Newer guidelines however suggest that symptomatic women who also require osteoporosis protection can be given HRT as first line treatment. Biphosphonates and other pharmacological agents are also effective in preserving bone density.
- The WHI study showed increased risk of CHD in women using conjugated equine oestrogen (0.625 mg) with or without progestogens, in the first 12 months of use [14]. It is now known that 'early harm' can occur when therapy is started in women over 60 years with relatively high doses. Therefore, if HRT is started after the age of 60, the minimum effective dose of oestrogen should be used. Data from the Danish Osteoporosis Study has shown an approximately 50% reduction in CHD risk if commenced within 10 years of menopause, hence referred to as the 'window of opportunity' for primary prevention [15]. The Kronos Early Estrogen Prevention Study showed a neutral impact on cardiovascular risk markers when HRT is commenced within three years of the last menstrual period [16]. Any cardio-protective benefit is not immediate and will be observed only after several years of use [17].
- There is conflicting evidence about starting HRT early and the protective effect on cognitive functions and possibly a reduction of long-term risk of Alzheimer's and other types of dementia. The WHI study failed to show any significant improvement in memory or cognitive function with HRT in older post-menopausal women. Therefore, based on current evidence the BMS does not recommend the use of HRT for the sole purpose of reducing the risk of dementia [13].
- WHI trial showed increased risk of stroke in women taking oestrogen alone or in combined therapy. However, the HERS study (the Heart and Estrogen progesterone Replacement Study) did not show a similar increase [18]. The evidence from observational studies is conflicting. Therefore, currently there is no evidence to recommend use of HRT for primary or secondary prevention of stroke. In women with an increased risk of stroke or thromboembolism, careful evaluation is required prior to commencement and transdermal routes should be preferred over the oral route if HRT is required [11].

HRT and cancer risk

The association between cancer and HRT has been a concern for many years. According to the WHI trial, there is a small increase in risk of breast cancer with use of oestrogen and progestogens for five years. The same study noted a small but significant reduction in risk with use of oestrogen alone. The Million Women Study also raised concerns over long term safety of HRT.

The WHI was the only study that assessed the association between HRT and ovarian cancer risk and it concluded that there was no increased risk. However, several case-control studies have suggested an increased risk with the use of oestrogen alone whereas no effect has been observed in combined therapy. A recent analysis of data from the Danish National Cancer registry also suggests a small increase in risk with either oestrogen or combined therapy. A recent individual patient meta-analysis that included over 12,000 women suggests a causal relationship, with one additional ovarian cancer per 1000 users and one ovarian cancer related death per 1700 users [19].

Endometrial cancer risk is greatest when oestrogen is used alone, which resulted in the recommendation of combined therapy many years ago. The risk of colorectal cancer is reduced with the use of oral combined HRT and this was evident in the WHI trial too. However, a similar effect was not observed with oral oestrogen alone and there is no data on colorectal cancer risk modification with other routes of administration.

The WHI trial showed no increase in the incidence of lung cancer with combined HRT but a higher risk of death from lung cancer, probably due to the effects on the outcome of non-small cell lung cancers [20]. However, the risk was not increased with oestrogen alone HRT [21].

HRT regimens

Sequential combined regimens should be used in women in the perimenopausal years or who have had their last menstrual period (LMP) within one year prior to starting HRT. Those who have had their LMP more than one year prior or those who have been on a sequential combined HRT for more than a year may start on continuous combined regimens if they do not wish to have withdrawal bleeds [11]. Often the side effects of HRT are due to progesterone and a solutions for this include reduction of duration in progesterone use (7-10 days) or use of a LNS-IUS (Mirena system), which can be used up to 4 years.

HRT in special cases

Cancer survivors pose a challenge with regard to HRT use. In treated endometrial cancer, studies have shown either a reduction or no increase in the risk of recurrence with use of HRT. However, much of this data has been from studies of early stage disease. Whether the

risk would be different in more advanced disease with microscopic deposits is not known. Local endometrial sarcomas are oestrogen sensitive and should be a contraindication for HRT. There is no evidence to suggest an increased risk of ovarian cancer recurrence and the same holds true for cervical cancer. Adequately treated squamous cell or adenocarcinoma of the cervix should not be considered a contraindication for HRT. There is no evidence of adverse events from use of either systemic or topical oestrogen following vulval carcinoma.

There is no conclusive evidence from clinical trials about the effects of HRT on breast cancer survivors. [22]. Those with hormone resistant (oestrogen receptor negative) cancers may consider HRT for troublesome menopause symptoms if they are resistant to other alternative therapies. They should be adequately counselled regarding the potential risks and lack of evidence prior to commencing treatment [23].

Alternatives to HRT

Selective serotonin reuptake inhibitors (SSRIs) and selective noradrenaline reuptake inhibitors (SNRIs) and gabapentin are effective in relieving vasomotor symptoms in the short term [24]. Their long term safety needs further evaluation. An oral selective oestrogen receptor modulator (SERM) ospemifene was recently approved by the Food and Drug Administration of USA as an orally active treatment for dyspareunia [12].

Other complementary alternative medicines and behavioural therapies have been proposed as interventions for alleviations of menopausal symptoms and they include non-hormonal agents such as phytoestrogens, black cohosh, and dehydroepiandrosterone as well as other modalities such as exercise, yoga and relaxation. All these lack robust scientific evidence at this point of time to make clinical recommendations [25].

In conclusion health care providers should be sufficiently equipped to deal with issues related to menopause and HRT plays an important role in their management. Since the evidence is fast evolving, recommendations of specialist organisations like the Sri Lankan Menopause Society are a useful tool for physicians [26].

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