Clinical case review

A 41-year-old woman with premature menopause

Commentary by **ALASTAIR MACLENNAN** MB ChB, MD, FRCOG, FRANZCOG

Should this woman be encouraged to continue hormone therapy (HT) until the normal age of menopause?

Case scenario

About six years ago, a 41-year-old patient presented with symptoms suggestive of menopause, which was confirmed by hormone assays (FSH 76 IU/mL, oestradiol <100 pmol/mL, progesterone 0.6 nmol/mL). She was euthyroid and not anaemic, and otherwise fit and well. She had never smoked and had two healthy daughters.

The patient was prescribed cyclical hormone therapy (HT), which she has used for six years. She says she feels 'much better' taking HT, but should she continue until the normal age for menopause?

The patient is reviewed regularly, and the results of a recent Pap smear, mammogram and bone mineral density assessment are normal. She has subsequently experienced a borderline elevation in her rheumatoid factor level, with moderate joint symptoms. She consulted a rheumatologist and was prescribed celecoxib; this provided good relief, but she needed 400 mg/day to achieve this.

Professor MacLennan is Professor of Obstetrics and Gynaecology, University of Adelaide, SA.

Commentary

It is very important that a woman with menopause at 41 years of age receives HT because she is at increased risk of premature osteoporosis, premature cardiovascular disease and premature dementia. Such women also suffer greater reductions in libido and in quality of life from menopausal symptoms, compared with those who experience menopause around the average age of 51 years. Thus, they are the most deserving of adequate HT, at least until the average age of menopause.

Premature menopause is uncommon, affecting 2% of women under 40 years of age and a larger group under 45 years who have a relatively premature menopause. Unfortunately, premature menopause is sometimes not recognised. Symptoms of oestrogen deficiency and menstrual irregularity are sufficient reasons for a trial of HT. A raised FSH level helps to confirm the diagnosis, but other hormone tests are unnecessary.

For the patient described above, who is now 47 years of age and has been taking cyclical HT for six years, appropriate advice could be to continue HT at least until the average age of menopause, and then to trial going without it every four to five years until she no longer has sufficient symptoms to warrant HT. There are no data to support slow weaning off HT. She should be counselled about the latest data on the risks and benefits of HT for women under 60 years of age (see the box on page 63).

Other options in this woman's therapy include changing to the lowest dose of combined continuous HT that keeps her asymptomatic. A continuous regimen should eliminate uterine bleeding over a few months, but women with premature menopause often need two to four times the oestrogen dose required by their older counterparts.

Future spontaneous cycles and occasional ovulation occur in around 17% of women with premature menopause, so infertility cannot be guaranteed. HT is not contraceptive, and if the small chance of pregnancy is a concern then a low dose combined oral contraceptive can be prescribed for a nonsmoker, which will double as HT. A regimen of continuous active pills is an option for avoiding a return of symptoms in the pill-free week.

If low libido is a complaint she could be given a trial of tibolone (Livial) or very low dose testosterone with the help of specialist advice (there are no products registered for use in women), as well as sexual counselling. Studies suggest that some women experience an improvement in arthritic symptoms when taking HT; the arthritis is not made worse and anti-inflammatory agents can sometimes be reduced.

In addition, women with premature

Insights from the Women's Health Initiative

It is important to understand that the only long term randomised controlled trial of HT, the Women's Health Initiative (WHI), initiated HT in mostly asymptomatic women aged 50 to 79 years (average age, 64 years).[1,2] An increase in the incidence of breast cancer was seen only in the group taking combined oestrogen and progestin HT and not in the hysterectomised group taking oestrogen only. The significant increase in breast cancer of 8/10,000 per annum (i.e. <0.01%) was first seen after five years of combined HT. There are no long term data from randomised controlled trials for women with premature menopause, but the increase in breast cancer seen after five years of combined HT in WHI was similar to that seen in women who experience menopause five years later than average. It is probably the extension of exposure to progestogens or progesterone beyond the average age of menopause that increases the risk of breast cancer. Observational data show that women using oral contraception or HT until age 50 years do not have a significant increased risk of cancers of the reproductive system, compared with nonusers who experience menopause around this age.[3,4]

Recent subanalyses of the WHI data suggest that there may be a critical window of therapeutic opportunity around and soon after menopause for cardioprotection – a significant reduction in cardiovascular events in younger women was observed when data from both HT arms (i.e. the combined oestrogen and progestin arm and the oestrogen only arm) were combined.[5] This fits well with recent animal and clinical studies showing that blood vessels and the brain are receptive to oestrogen for a few years after menopause.[6,7] At this time, oestrogen can inhibit the progression of atherosclerosis and may also be neuroprotective. This effect is lost if HT is commenced in late menopause, so it is especially important to treat women with premature menopause early and at least until they are aged 51 years or become asymptomatic.

Bar a small absolute risk of thromboembolism, women who initiated HT near menopause had no increase in serious morbidities in the WHI study.

menopause sometimes have psychological concerns about their premature loss of fertility and ovarian hormones. Referring them to further information may be useful (e.g. www.early menopause.com).

Final comments

It is the untreated woman with premature menopause who is at greatest risk of reduced quality of life and increased risk of chronic disease. No substitutes for HT have been proven to be superior in placebo controlled or head to head trials for control of menopausal symptoms. In particular, phytoestrogens and herbal supplements have not been shown to provide adequate protection or to have long term safety or efficacy in the management of premature menopause. Although there are other therapeutic policies and lifestyle issues to help control bone loss and to reduce cardiovascular risk and cognitive decline, none would be as comprehensive, simple, inexpensive, efficient and safe as oestrogen therapy in otherwise healthy women under the age of 50 who have experienced premature menopause. To ignore a patient's severe menopausal symptoms and risk of possibly preventable chronic disease and not to offer HT because of the risk profile described in women initiating HT much later in life would not be reasonable care. MT

References

1. Rossouw JE, Anderson GL, Prentice RL, et al; 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: 321-333.
2. Anderson GL, Limacher M, Assaf AR, et al; 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: 1701-1712.
3. Deligeoroglou E, Michailidis E, Creatsas G. Oral contraceptives and reproductive system cancer. Ann N Y Acad Sci 2003; 997: 199-208.
4. Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and hormonal contraceptives: further results. Contraception 1996; 54(3 Suppl): 1S-106S.
5. Salpeter S. Hormone therapy for younger women: how can we make sense out of the evidence? Climacteric. In press 2005.
6. MacLennan AH, Sturdee DW. Towards safer women, safer doses, safer routes and safer timing of administration of safer menopausal therapies. Climacteric 2005; 8: 1-2.
7. Phillips LS, Langer RD. Postmenopausal hormone therapy: critical reappraisal and a unified hypothesis. Fertil Steril 2005; 83: 558-566.

DECLARATION OF INTEREST: Professor MacLennan is solely employed by the University of Adelaide. He has, through the university, received research funds for clinical trials of new pharmaceutical products and has had expenses from the manufacturers for invited lectures.

Who wants your opinion?

WE DO. Did you find a particular article in this issue helpful in your practice? Do you have something to say about an article we have published or some of the opinions expressed? Write and tell us, and we will consider your letter for publication. We are more likely to print short letters (no longer than 250 words), so please be succinct.

Write to: Medicine Today,
PO Box 1473, Neutral Bay NSW 2089.