Managing the menopause what to do now

The recent Women's Health Initiative (WHI) study has not significantly changed how women with menopausal problems should be managed or informed. The cornerstone of management remains the comprehensive evaluation of the individual woman, including a careful history and examination, a risk–benefit analysis and lifestyle advice coupled with accurate information regarding her therapeutic options.

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The enormous media response to the recently terminated US Women's Health Initiative (WHI) study of the use of continuous-combined conjugated equine oestrogens 0.625 mg and medroxyprogesterone acetate 2.5 mg long term in healthy postmenopausal women has ranged from thoughtful to sensational. Panic was caused, numerous women discontinued therapy, and women and their health providers alike have been thrown into a state of confusion, distrust and quandary of what to do next.

The merits and demerits of the data and the wisdom of the decision to terminate this arm of the WHI study is the subject of much debate. In clinical practice, most women with the characteristics of the WHI women are not treated with that particular hormone therapy preparation. Furthermore, in clinical practice, most women with menopausal complaints are not from the population demographic examined by WHI.

Definitions, symptoms and physiology

Menopause is a retrospective diagnosis made after 12 months of amenorrhoea following a final menstrual period. It reflects a near complete but natural diminution of ovarian hormone secretion and usually occurs between the ages of 42 and 58 years. The mean age is 51.3 years.[1]

Some women start to experience various menopausal symptoms, including vasomotor symptoms, breast tenderness, insomnia, migraines and premenstrual dysphoria, in the few years before their final menstrual period. In the late menopausal transition, usually after the final menstrual period, genital atrophic symptoms and problems in sexual function can also occur.

IN SUMMARY

- **The findings of the Women's Health Initiative study have not significantly changed how women with menopausal symptoms should be managed or informed.**
- **Menopause medicine is growing more complex, and pharmacotherapeutic options are broad and not always necessary.**
- **Lifestyle evaluation and advice remains the cornerstone of advice for the mid-life woman.**
- **Each individual woman must undergo a careful assessment and a risk–benefit analysis before she is prescribed hormone therapy (HT).**
- **The two specific indications for the use of HT are menopausal symptoms and significant bone loss.**
- **HT is not recommended for either primary or secondary cardiovascular disease prevention.**

Not all women have symptoms as they transition to the menopause. Those with symptoms experience them in different combinations and levels of intensity.[1]

Menopausal symptoms are subjective by their nature, making quantification difficult. Symptomatology varies markedly among different ethnic groups, cultures, socioeconomic groups, and even climates. During the menopausal transition, symptoms do not track closely with the menstrual cycle or with endocrine changes.

The menopause transition or perimenopause

The menopausal transition, or perimenopause, is defined by menstrual cycle and endocrine changes. Perimenopause literally means about or around the menopause. The menopausal transition usually begins with variation in the menstrual cycle with cycles of more than seven days difference from the normal cycle and/or two or more skipped cycles. Menstrual flow changes can be highly variable. The menopause transition lasts an average of four to six years from the onset of irregular menses or symptoms.

Follicle stimulating hormone (FSH) is the first measurable sign of reproductive ageing but must be obtained between days 2 and 5 of the cycle. While periods are regular, FSH levels will often be in the normal range. FSH levels gradually rise during the menopausal transition, but the variability is high.[1] In view of this, FSH measurements should be undertaken only in women in whom the diagnosis is clinically in doubt.

The term 'climacteric' is a popular and synonymous term with perimenopause. Generally this term is used with, and by, patients and in the lay press.[1]

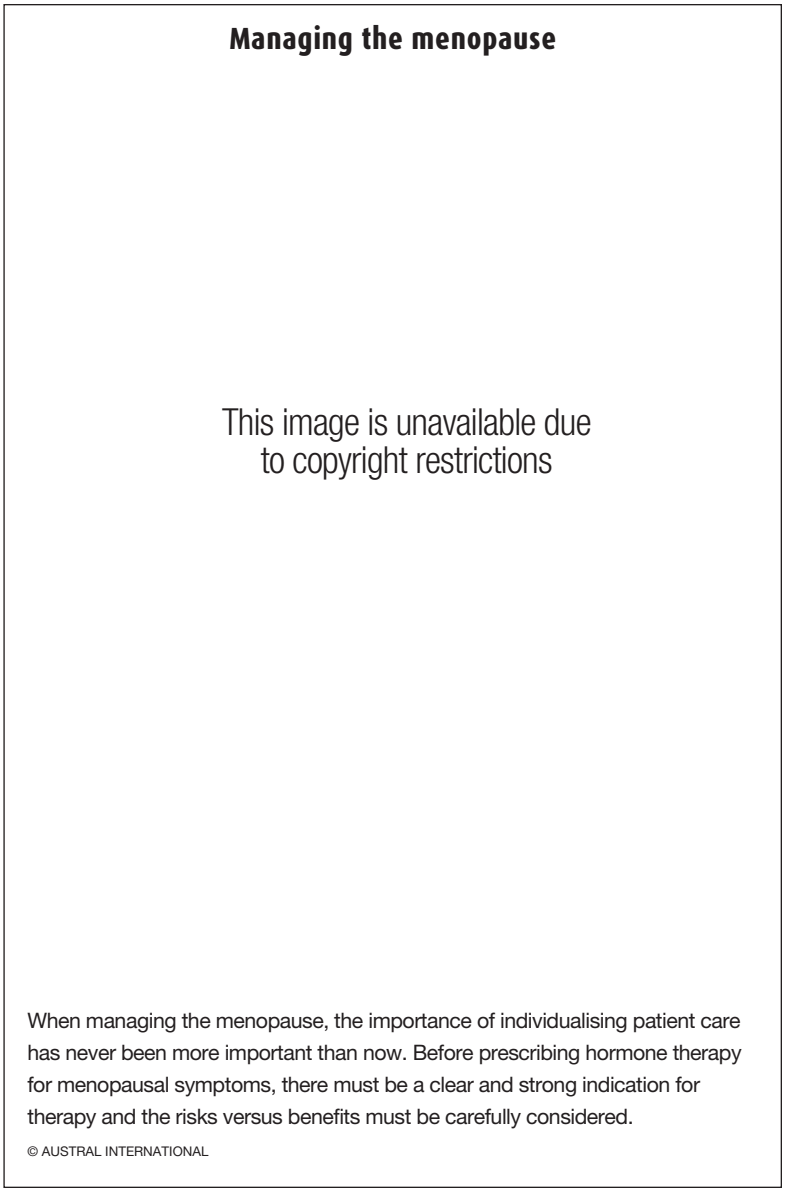
The early postmenopause

The early postmenopause is defined as the two to five years following the final menstrual period. During this time there is a further dampening of ovarian hormone function to a permanent level as well as a period of accelerated bone loss.[1]

The WHI study

A component of the WHI study – a large, multicentre major clinical trial sponsored by the US National Institute of Health – was set up to evaluate the risks and benefits of conjugated equine oestrogens 0.625 mg/day and medroxyprogesterone acetate 2.5 mg/day in healthy postmenopausal women. It was a placebo-controlled, primary prevention, randomised, controlled trial of 16,608 postmenopausal women aged 50 to 79 years (mean age 63) with an intact uterus. The trial was stopped after a mean of 5.2 years as the health risks were deemed to exceed the benefits. Another arm of this study, investigating the use of oestrogen or placebo alone in women who have had a hysterectomy, is continuing.

Managing the menopause



When managing the menopause, the importance of individualising patient care has never been more important than now. Before prescribing hormone therapy for menopausal symptoms, there must be a clear and strong indication for therapy and the risks versus benefits must be carefully considered.

Of the study population, 70% had a body mass index (BMI) greater than 25, with 34% having a BMI greater than 30. Overall, one-third was hypertensive and 40% had been smokers. Clearly, this is not the normal population prescribed hormone therapy (HT) in Australia. There was a high discontinuation rate in the oestrogen and progestin arm (42%) and crossover to the treatment arm from placebo was high at 10.7%.

The study was reported using percentiles of relative risk, rather than the pertinent issue to women, absolute risk. A review of the *Journal of the American Medical Association* article demonstrates absolute risk to be low, invariably a fraction of 1%. Thus, the widely reported 26% relative increase in invasive breast cancer translates into 38 cases among HT users versus 30 cases among placebo users per 10,000 women per year. Similarly (and as shown in Table 1):

- the 29% increase in coronary heart disease (CHD) translates into 37 cases in HT users versus 30 cases in placebo users/10,000 women/year
- the 41% increased risk of stroke corresponds to 29 cases in HT users versus 21 in placebo users/10,000 women/year
- the 111% increased risk of venous thromboembolism corresponds to 34 cases in HT users versus 16 in placebo users/10,000 women/year.

On the benefit side:

- the 33% reduction in hip fracture translates to 10 cases in HT users versus 15 in placebo users/10,000 women/year
- the 37% reduction in colorectal cancer translates to 10 in HT users versus 16 in placebo users/10,000 women/year.

There was no difference in total mortality in either group.

What do these findings mean?

The clinical relevance of the WHI study findings is as follows:

- Continuous-combined conjugated equine oestrogen and medroxypro - gesterone acetate is of no value in reversing established CHD or in preventing CHD in apparently healthy women.
- Continuous-combined conjugated equine oestrogen and medroxypro - gesterone acetate increases the risk of myocardial infarction, deep venous thrombosis and thromboembolism, particularly in the first 12 to 18 months of therapy. The stratification of individual risk should be based on classical risk factors and algorithms (for further information on coronary risk assessment, see the website of the International Task Force for Prevention of Coronary Heart Disease at: www.chd-taskforce.de).
- The slight increase in invasive breast cancer occurs earlier than anticipated from observational studies (i.e. within five years of HT use). The increase was marked at year four, with a trend to a later decline in number of events. This would appear to confirm that HT provides a growth-promoting rather than a causative role in breast cancer; however, with the premature termination of the study, this question was not answered.

Clinicians select the HT type on the basis of women's characteristics, needs and preferences. In clinical practice, most women with the characteristics of the WHI women are not treated with the HT preparation used in the study. The WHI results, and particularly the data on cardiovascular disease risk, should only be related to the continuous-combined treatment of 0.625 mg conjugated equine oestrogen and 2.5 mg medroxyprogesterone acetate, prescribed to elderly, obese women with characteristics similar to those depicted in the WHI study.

The results of the WHI study do not give any indication of the possible effects of other doses of conjugated equine

Table 1. Summary of findings from the WHI study*

Outcome	Excess number of cases/10,000 women/year	Cases in women taking oestrogen plus progestin (n=8506)†	Cases in women taking placebo (n=8102)	Adjusted 95% confidence intervals
CHD	+7	164	122	0.85-1.97
Stroke	+8	127	85	0.86-2.31
Pulmonary embolism	+8	70	31	0.99-4.56
Invasive breast cancer	+8	166	124	0.83-1.92
Colorectal cancer	-6	45	67	0.32-1.24
Hip fracture	-5	44	62	0.33-1.33

* Adapted from reference 2. † 0.625 mg conjugated equine oestrogen plus 2.5 mg medroxyprogesterone acetate.

oestrogen or medroxyprogesterone, routes of administration, formulations or the use of progestins alone. With respect to most other combinations of oestrogens and progestins, there are no equivalent epidemiological investigations at hand.

A word about WISDOM

In mid-July 2002, an independent safety panel for the Women's International Study of Long Duration Oestrogen after Menopause (WISDOM) unanimously concluded that WHI's evidence that HT increases the risk of heart disease was not convincing. The WISDOM Trial's Steering Committee decided to continue with the study, which had already started in the UK and Australasia and was designed to include overall a younger group of women than the WHI study and to continue until 2016. The study design was similar to that of WHI, but would include quality-of-life and dementia end points. In October of this year the study was terminated by an independent review committee; however, this was not for safety reasons.

Management options

Menopause medicine is growing more complex, and pharmacotherapeutic options are broad and not always necessary. HT still has its primary indication for relief of climacteric symptoms (hot flushes, sweats, insomnia and urogenital atrophy). There are no equally effective alternatives. However, after two years of HT, each individual woman should, after consultation with her doctor, reconsider the merits of continuing this treatment. Tables 2, 3 and 4 list the various HT preparations that are available in Australia and indicated for menopausal symptoms.

HT remains suitable for the treatment of severe osteopenia and osteoporosis without fracture, the WHI study having shown a reduced fracture risk with treatment.

The boxes on page 23 provide some suggestions for rural and remote GPs in managing menopause, a menopause management summary and a list of useful websites for doctors and their patients.

Lifestyle assessment

Lifestyle evaluation and advice remains the cornerstone of advice for the midlife woman. Taking a careful history, including past, psychosocial, sexual and family history, in addition to conducting an examination, is mandatory, as is evaluating lifestyle risk factors. A dietary history, including calcium intake, must be taken, as well as obtaining details on physical activity, smoking and alcohol intake. BMI should also be evaluated. Appropriate advice should be given.

Women should keep to the regular schedule of mammograms and breast self-examinations, to aid early detection of breast cancer, and have regular Pap smear examinations. Regular review of cardiovascular health, including blood

Table 2. Combination HT preparations available in Australia

Regimen	Type of oestrogen and progestin	Product	Formulation
Cyclic regimen (oestrogen 11 days, oestrogen plus progestin 10 days, 7 therapy-free days)	Cyproterone acetate, oestradiol valerate	Climen	Tablets
Continuous-cyclic regimen (oestrogen daily, progestin 10-14 days)	Cyproterone acetate, oestradiol valerate Dydrogesterone, oestradiol Medroxyprogesterone acetate, conjugated oestrogens Norethisterone acetate, oestradiol	Climen 28 Femoston Menoprem Premia Estalis Sequi Estracombi Trisequens	Tablets Tablets Tablets Tablets Transdermal patches Transdermal patches Tablets
Continuous-combined regimen (oestrogen and progestin daily)	Medroxyprogesterone acetate, conjugated oestrogens Norethisterone acetate, oestradiol	Menoprem Continuous Premia Continuous Provelle 28 Estalis Continuous Kliogest Kliovance	Tablets Tablets Tablets Transdermal patches Tablets Tablets

pressure measurement and lipid profiles, should be conducted regularly.

Hormonal therapies

Oestrogens and progestins

Cyclical HT

In the perimenopause and immediate postmenopause (two to three years after the final menstrual period) oestrogen and cyclical progestin therapy should be prescribed. This may lead to a regular cyclical withdrawal bleed. Continuous-combined therapy is not prescribed as it can lead to irregular or breakthrough bleeding due to erratic diminishing ovarian function.

HT should be started at the lowest possible effective dose. The older the woman, the more slowly the therapy should be started. A minimum of 10 to 14 days of progestin monthly is recommended to protect the endometrium. Women who require long term therapy should be switched to a continuous-combined regimen to protect their endometrium in the longer term once they are established in the postmenopause.

It is important to note that with long term use, long-cycle therapy – i.e. progestin administered every two to three months – increases the risk of endometrial pathology, including hyperplasia and malignancy.

Table 3. Oestrogen and progestin preparations available in Australia

Hormone	Product	Formulation
Oestrogens		
Oestradiol	Climara	Transdermal patch
	Dermestril	Transdermal patch
	Estraderm, Estraderm MX	Transdermal patch
	Femtran	Transdermal patch
	Menorest	Transdermal patch
	Estrofem	Tablets
	Zumenon	Tablets
	Natragen Cream (WA only)	Cream
	Oestradiol Implants	Implant
	Sandrena	Gel
Oestradiol valerate	Progynova	Tablets
Oestriol	Ovestin Tablets	Tablets
Oestrogens, conjugated	Premarin	Tablets
Piperazone oestrone sulfate	Genoral	Tablets
	Ogen	Tablets
Progestins		
Cyproterone acetate	Androcur	Tablets
	Cyprone	Tablets
	Cyprostat	Tablets
	Procur	Tablets
Dydrogesterone	Duphaston	Tablets
Medroxyprogesterone acetate	Medroxyhexal	Tablets
	Provera	Tablets
	Ralovera	Tablets
Norethisterone	Primolut N	Tablets
Progesterone	Pro-Feme Cream (WA only)	Cream

Table 4. Other HT used for menopause

Generic name	Product	Formulation
Tibolone	Livial	Tablets
Testosterone	Andro-feme Cream (WA only)	Cream

Continuous-combined HT

Continuous-combined HT should be prescribed after the immediate postmenopause and has the advantage of producing amenorrhoea. In women requiring long term HT, the minimum effective dose should be prescribed. With increasing duration of therapy, it may be possible to reduce the effective dose required.

Modes of administration

- **Oral.** Oral therapies should be initiated in the first instance. Various formulations, either singly or combined and for either cyclical or continuous-combined use, are available.
- **Transdermal.** Oestrogen patches and oestrogen and progestin patches combined in a single patch are available. The latter are available as either continuous-cyclic or continuous-combined preparations. Transdermal administration is preferable to oral therapy in women with hypertriglyceridaemia, a history of migraine without focal symptoms and where there is a past history of a provoked venous thromboembolism (i.e. associated with trauma or surgery) without evidence of a coagulopathy. These women may require specialist referral. Oestradiol gel is an

alternative method of oestrogen administration. Other percutaneous creams, particularly progesterone creams that are compounded, have been shown to be poorly absorbed and do not confer endometrial safety.

- **Transmucosal.** Transmucosal therapies in the form of lozenges (troches) are individually compounded; there are no safety or efficacy data on these preparations. As these preparations are biologically active, the side effect profile and long terms risks should be considered as being similar to all other hormonal therapies. In particular, endometrial, cardiovascular and breast safety are not established.
- **Intranasal.** Intranasal oestrogen and progestin preparations are currently being trialled.
- **Vaginal.** Vaginal oestrogen preparations may be used for the treatment of genital atrophic symptoms, including vaginal dryness and loss of lubrication with intercourse.

Unopposed oestrogens

Unopposed oestrogens are normally prescribed to women who have had a hysterectomy. They may be used also in very selected women who are intolerant to progestins. Ideally, these women who have an intact uterus should be under the care of a gynaecologist and have regular endometrial assessments by transvaginal ultrasound and endometrial biopsy.

Testosterone

Testosterone therapy is controversial and should be considered only in the setting of testosterone deficiency. Serum testosterone assays are neither sensitive nor specific enough for use in women.

If ordered, a serum testosterone level

Suggestions for rural and remote GPs

- Develop and maintain skills in the investigation of abnormal uterine bleeding.
- Have a contact list for menopause specialists in your State or Territory.
- Use websites and email for advice for difficult cases and self-education.
- Use electronic media for the promotion of patient education and consider involving community nurses and/or health workers in community education projects.

Useful websites for practitioners and patients

Australasian Menopause Society
www.menopause.org.au
Jean Hailes Foundation
www.jeanhailes.org.au
International Menopause Society
www.imsociety.org
North American Menopause Society
www.menopause.org

Menopause management summary

- Establish the patient's reasons for consultation.
- Determine the patient's risk factors.
- Decide which investigations are appropriate.
- Assess the patient's individual risk–benefit analysis.
- Provide advice on recommended lifestyle interventions.
- Decide whether hormone therapy is indicated.
- Give current evidence based information regarding menopause management.
- Discuss individualised management options.
- Facilitate a therapeutic relationship and maintain regular follow up.

should be used in conjunction with serum sex hormone binding globulin (SHBG) assay and a free androgen index (FAI). Some laboratories use a sensitive testosterone assay, which is able to detect lower testosterone levels. Women who are still menstruating should have their levels measured after day 7 of their cycle and the sample taken in the morning. Women with levels in the lower third of the normal range can be considered for testosterone replacement therapy. In women who are still menstruating, testosterone can be given alone. In women after the menopause, testosterone therapy should be administered only with oestrogen and, when appropriate, progestins.

The aim of therapy is to achieve testosterone levels in the upper third of the normal range. At present, no testosterone therapy has been specifically approved Australia-wide for use in women, but in several centres, a trial of testosterone by injection is used to assess the response to therapy.

Testosterone implants have been used for many years as the mode of treatment in the longer term. Testosterone 1% cream (Andro-Feme Cream, currently available only in Western Australia) can be used as an alternative. The testosterone patch is unsuitable for use in women and should only be used in men; however, a patch designed for women is in the research phase. The safety and efficacy of oral testosterone in women has not been determined.

Tibolone

Tibolone (Livial) is a tissue-specific therapy with effective modes of action that improve menopausal symptoms and maintain both spine and hip bone density. There are three metabolites; two are oestrogenic and the third has a progestogenic and androgenic action. No added progestin is required. Tibolone metabolites block sulfatase action *in vitro* and cause less breast tenderness and mammographic density compared with standard oestrogen plus progestin therapy. No breast cancer risk data or fracture risk data are yet available.

Nonhormonal therapies

Complementary therapies

Up to 50% of postmenopausal women use over-the-counter therapies, including those marketed for menopausal management. Several small studies have been performed on various phytoestrogen products and shown inconsistent results. Most have shown no difference in improvement between the phytoestrogen preparation and placebo – roughly a 40% improvement. Phytoestrogen absorption and metabolism is extremely variable and is dependent on many factors.

Low dose SSRIs

Some studies have shown a reduction in hot flushes with the use of the SSRI venlafaxine (Efexor) at doses of 75 to 150 mg/day. This therapy should be started slowly with a gradual increase to the appropriate dose.

Clonidine

Clonidine (Catapres 100) has been used for many years in the treatment of hot flushes but is usually discontinued because of side effects.

Propranolol

Propranolol (Inderal, Deralin) is similar to clonidine in its effectiveness for menopausal symptoms but has been used less often.

When to refer

Women should be referred to a specialist if they have:

- menopausal symptoms and a complex medical history
- abnormal uterine bleeding
  - before therapy
  - while taking cyclic therapy
  - while taking continuous-combined therapy and that is excessive, that occurs after a significant period of amenorrhoea on therapy, or that lasts longer than the initial six months of therapy
- symptoms that are unrelieved by standard HT
- persistent side effects from therapy but require menopausal treatment.

Conclusions

In the management of the menopause, the importance of individualising patient care has long been emphasised. Never has it been more important than now. Before prescribing HT, there must be a clear and strong indication for therapy, and the risks versus benefits carefully considered. Short term therapy for symptoms still necessitates careful monitoring. Longer term therapy, now probably defined as beyond two years, mandates even more rigorous monitoring and an annual risk-to-benefit evaluation. MT

References

1. Executive summary: stages of reproductive aging workshop (STRAW), Park City, Utah, July 2001 [Workshop report]. Menopause 2001; 8: 402-407.

2. Writing group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women. JAMA 2002; 288: 321-333.