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Hormone therapy

Where are we now?

Background

Menopause is the permanent cessation of menstruation resulting from loss of ovarian follicular activity. The characteristic symptoms of a fall in oestrogen are vasomotor and urogenital atrophy symptoms; with symptoms reported by up to 85% of women over a mean duration of 5.2 years. Long term consequences of menopause include osteoporosis and cardiovascular disease. Menopause management is highly controversial and can be confusing for both clinicians and their women patients.

Objective

To explore menopausal management options including comprehensive evaluation; lifestyle modification for symptom relief and risk prevention; hormone therapy or nonhormonal alternatives for symptom relief; prevention and treatment of long term risks; and education and psychological support and therapy.

Discussion

Use of hormone therapy involves consideration of the woman's risk-benefit profile. We attempt to clarify this complex topic and focus on the impact of hormone therapy in women aged 50–59 years, including the benefits of relief of hot flushes and urogenital atrophy symptoms and the prevention of fractures and diabetes; and the risks, including venothrombotic episodes, stroke, cholecystitis and breast cancer (with combined oestrogen and progestogen only). Nonhormonal options are also explored.

Keywords: menopause; hormone therapy

CPD

Menopause is the permanent cessation of menstruation resulting from loss of ovarian follicular activity and is diagnosed retrospectively following 12 months of amenorrhea in association with elevated gonadotrophins and oestrogen deficiency.[1] Premature menopause occurs before the age of 40 years and early menopause before 45 years. Menopause can be spontaneous or can be induced by chemotherapy, radiotherapy or surgery. The time leading up to the menopause – the menopause transition – is characterised by declining ovarian follicle numbers, menstrual irregularity and hormonal changes including increasing follicle stimulating hormone, decreasing inhibin B and anti-mullerian hormone, and variable oestradiol levels.[2] Testosterone levels decline during early to mid reproductive life with little change during the menopause transition.[3] The average age of spontaneous natural-age menopause is 51 years, with the menopause transition commencing at 47.5 years. Risk factors associated with an earlier menopause include smoking, positive family history and pelvic surgery (including hysterectomy).[4]

Menopause symptoms

The characteristic symptoms of oestrogen deficiency are vasomotor and urogenital atrophy symptoms (including vaginal dryness and dyspareunia), however a range of other symptoms can occur. Symptoms associated with natural menopause usually commence during the menopause transition and are reported by up to 85% of women, with 10–20% reporting severe symptoms. The mean duration of vasomotor symptoms in the Melbourne Women's Midlife Health Project cohort was 5.2 years with 23% of women reporting flushing at year 13 of follow up.[5] A number of factors, including age, cause of menopause, levels of anxiety, and socioeconomic and cultural factors influence the menopausal experience.

Women diagnosed with breast cancer may experience menopausal symptoms secondary to:

- diagnosis of breast cancer occurring concurrently with natural menopause
- withdrawal of hormone therapy (HT) following breast cancer diagnosis

- menopause induced by breast cancer treatment (GnRH agonist therapy, oophorectomy or chemotherapy), and
- as side effects of adjuvant therapy (tamoxifen and aromatase inhibitors).

Sexual dysfunction is reported by up to 88% of perimenopausal women and encompasses problems with desire/libido, arousal, orgasm and sexual pain.[6] However, women are often reluctant to disclose urogenital symptoms or sexual dysfunction. Anxiety and depression is common in Australian women, and these symptoms may increase during the menopause transition.[5] More severe symptoms are experienced by younger women, or women with surgical menopause or a diagnosis of breast cancer.

Long term consequences of menopause

Cardiovascular disease (CVD) is the leading cause of death in Australian women, occurring predominately in postmenopausal women. Osteoporosis is primarily a disease of postmenopausal women, with 56% of women aged over 60 years projected to sustain osteoporotic fractures.[7] Premature menopause is associated with increased risk of CVD, osteoporosis, cognitive dysfunction, Parkinson disease, dementia and overall mortality.[8] Trials have found that oestrogen may decrease some of the risks associated with premature menopause.[8]

Management of menopause

Management of the menopause includes:

- lifestyle modification: including prevention of further weight gain, weight loss (if required) through physical activity, and regulation of energy intake assists menopausal and psychological symptom control and CVD and osteoporosis prevention
- education: with reference to the woman's understanding of, and attitude toward, menopausal issues, cultural beliefs, in addition to expectations and concerns regarding the potential therapies available
- exploring, evaluating and managing psychological issues relevant to the woman
- the use of HT and nonhormonal treatments in the management of symptoms
- prevention/treatment of long term menopause related conditions.

Hormone therapy

The risks and benefits of HT are complex and the literature addressing this area is vast and often confusing. The term hormone therapy is used here to refer to oestrogen, either alone (ET) or in combination with a progestogen (EPT). Observational studies, predominately conducted in symptomatic women close to the time of menopause, suggested that HT reduced CVD and osteoporosis but increased venous thromboembolism and breast cancer risk (EPT). However, the Women's Health Initiative (WHI) randomised controlled trial of EPT indicated adverse cardiovascular and breast cancer outcomes.[9] Many HT users subsequently ceased HT, often without medical consultation, and women were reluctant to commence, or doctors to prescribe, HT.

The WHI trial involved largely older women (average age 63 years) without menopausal symptoms and understanding of the impact of HT in the initial 5 years postmenopausal (when HT use is most relevant) was advanced little by this study. Recently, the United States Endocrine Society published a scientific statement to assist clinicians with data interpretation and provide evidence based recommendations, including evaluation of the evidence quality (*Table 1*).[10] The major conclusions from this review regarding women aged 50–59 years were expressed as the number of women/1000 taking HT for 5 years who would experience benefit or harm (*Figure 1*).

Primary benefits included relief of hot flushes and urogenital atrophy symptoms and prevention of fractures and diabetes. Risks included venothrombotic episodes, stroke and cholecystitis. In this subgroup, EPT increased the risk of breast cancer, whereas ET alone did not. Beneficial effects on colorectal and endometrial cancer and harmful effects on ovarian cancer occurred but affected only a small number of women. Thus, data from the various WHI studies may not be applicable and must be interpreted with caution in relation to HT risks/benefits in women starting HT shortly after menopause.

Current indications and contraindications for systemic HT are summarised in *Table 2*. However, the woman's individual risk-benefit analysis should always be considered.

Vaginal oestrogen is the preferred therapy for isolated urogenital symptoms. Although use of vaginal oestrogens has been considered to be associated with minimal systemic absorption, their use in women taking aromatase inhibitors is controversial.[11] Vaginal oestrogen therapy and systemic HT may be used concurrently where there is inadequate control of urogenital symptoms with systemic therapy alone.

Tibolone, a synthetic steroid whose metabolites have oestrogenic, progestogenic and androgenic properties, is an alternative to conventional HT. Tibolone has positive effects on vasomotor and urogenital symptoms, sexual function, bone density and fracture risk. Tibolone use is associated with less mastalgia and abnormal uterine bleeding compared with conventional HT. There may be less oestrogenic effect on mammographic density, venous thromboembolism and lipid metabolism. Further research is required. No increased risk of breast cancer or endometrial hyperplasia/carcinoma was observed in randomised controlled trials of up to 4 years duration; however, data regarding the long term safety of tibolone is limited.

'Bio-identical' hormones contain active hormones with both benefits and side effects likely to be similar to conventional HT, however, there are potentially greater risks with these preparations as they are individually compounded with little safety monitoring and regulation.[12] Prescription of bio-identical hormones is not currently recommended until there is sound pharmacokinetic, efficacy and safety data. The US Food and Drug Administration has taken action

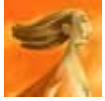

Table 1. Benefits and risks of hormone therapy[10]

Summary of evidence for key hormone therapy outcomes

Symptom benefits

- Flushes: ET + EPT + tibolone improve hot flushes (A)
- Vaginal symptoms: vaginal and systemic oestradial improves vaginal atrophy, reduces overactive bladder symptoms and urinary tract infections and tibolone improves urogenital atrophy (A)
- Mood: HT improves health related quality of life and possibly mood (B)
- Sexual function: tibolone induces improvements in desire, arousal, satisfaction, and receptiveness (B)

Long term benefits

- Fractures
  - ET/ERT prevents hip and spine fractures
  - tibolone reduces fractures in osteoporotic women over 60 years of age (A)
- Colon cancer: EPT (A) and tibolone (B) decrease colon cancer
- Breast cancer: tibolone reduces the risk of developing breast cancer (B)
- Mortality: HT is associated with a 40% reduction in mortality in younger postmenopausal women (B)

Neutral

- Cognition: after menopause, HT probably has no effect on midlife cognitive function (B)
- Symptoms: vaginal oestrogen twice weekly does not stimulate the endometrium (B)
- Thrombosis: transdermal oestrogen does not increase venothrombotic episode risk (C)
- Cardiovascular
  - low dose oestrogen therapy does not increase stroke risk (C)
  - tibolone does not increase the risk of coronary heart disease (B)
  - basic science, animal models, and observational studies suggest that HT reduces CVD, while interventional trials suggested harm in older postmenopausal women (B)

Risks

- Thrombosis: EPT and raloxifene increase venous thrombosis approximately twofold multiplicative with baseline risk factors including age, higher body mass index, thrombophilias, surgery, immobility (A)

Breast cancer

- Tibolone increases risk of breast cancer recurrence (A)
- ET increases the risk of breast cancer after more than 5 year of use (B)
- EPT increases invasive breast cancer risk, which may occur within 3–5 years of initiation and rises progressively beyond that time (B)
- For the subgroup of first time hormone users of EPT the overall WHI data indicate no increased breast cancer risk after 5.2 years, particularly in those starting HT several years after the onset of menopause (B)
- The risk of breast cancer in association with ET and EPT returns to approximately that of nonusers within 3–5 years of cessation (B)
- Rapid declines were noted in incidence of oestrogen receptor-positive breast cancer, which was temporally associated with a decline in use of HT after WHI reports (B)
- Linear models suggest a 3% relative increase in breast cancer per year of exposure in thin women and a lesser risk in obese women (C)
- No single estimate of absolute risk of breast cancer can be provided for an individual woman because risk varies with time of initiation relative to final menses, duration of use, and body mass index and, possibly, with type of progestogen and family history of breast cancer (C)

Others

- Cognition: HT initiated after about 65 years of age increases risk of dementia (B)
- Stroke: standard dose oral HT may increase stroke risk in healthy women (B)
- Ovarian: long term oestrogen therapy (alone) is associated with a small risk of ovarian cancer
- ET alone increases endometrial cancer and EPT increases gallbladder disease (A)

Level of evidence A = based on randomised controlled trial data and meta-analyses and unlikely to change
Level of evidence B = quality evidence that may change
Level of evidence C = low quality evidence that may change

over bio-identical hormones and announced that it considers the term 'bio-identical' a marketing term and not one of scientific or medical merit with claims made about safety and efficacy of compounded bio-identical hormones considered false and misleading.

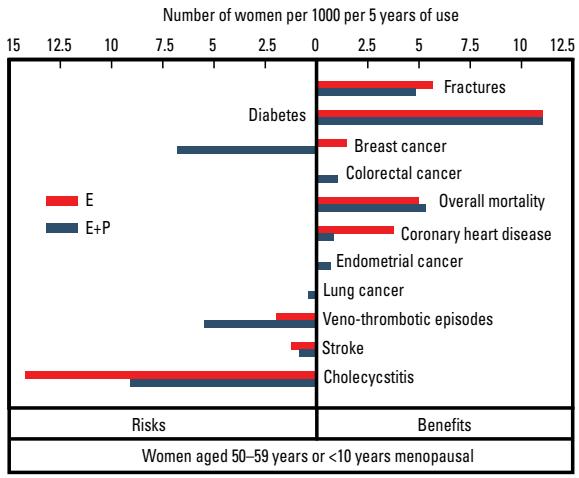

Figure 1. Risks and benefits of HT in women starting HT between the ages of 50–59 years or <10 years after the start of menopause
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Nonhormonal pharmacological therapies

Nonhormonal therapies include a range of selective serotonin reuptake inhibitors/serotonin noradrenalin reuptake inhibitors, vitamin E, gabapentin and clonidine have been evaluated in regard to treatment of vasomotor symptoms, primarily in women with breast cancer, with a meta-analysis concluding that paroxetine, venlafaxine, gabapentin and clonidine were effective in reducing vasomotor symptoms.[13] However, these studies were of short duration and long term efficacy and safety are unknown.
As paroxetine and fluoxetine may interfere with tamoxifen metabolism, these medications should be avoided in women taking tamoxifen.[11] Nonhormonal therapy for urogenital atrophy consists of vaginal moisturisers, used daily to improve symptoms, and lubricants, used before sexual intercourse.

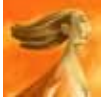
Nonpharmacological alternative therapies are discussed further in the article by Emma Warnecke in this issue of *Australian Family Physician*.

Conclusion

Managing menopause can be challenging for both the woman and her GP. Recent clarification of the risk-benefit of HT assists decision making and individualisation of therapy. Lifestyle measures and education remain keystones of management (see *Resources*). Further research is needed to clarify the role of alternative therapies.

Table 2. Indications and contraindications for hormone therapy

Indications for hormone therapy	
Relief of menopausal symptoms	HT is the most effective therapy for menopausal vasomotor and urogenital symptoms
Treatment of premature menopause	Observational evidence indicates that the use of HT in women with premature/early menopause negates or minimises increased risks and improves menopausal symptoms
Consider in a women aged less than 60 years with low bone density without fracture	Observational and randomised controlled trial evidence indicates that HT increases bone mineral density and decreases fracture risk. Consider the individual's risk-benefit profile
Contraindications to hormone therapy	
Absolute	**Relative contraindication** – seek specialist advice
Current or suspected breast cancer	Past history of breast, endometrial or ovarian cancer
Current endometrial cancer	Increased risk of venous thromboembolism
Unexplained vaginal bleeding	Previous ischaemic heart disease
Acute ischaemic heart disease	Focal migraine
Active liver disease	Hypertriglyceridaemia
Cerebrovascular disease	
Current deep vein thrombosis/pulmonary embolism	
Active systemic lupus erythematosis	
Pregnancy	



Resources

- Jean Hailes Foundation: www.jeanhailes.org.au
- Australian Menopause Society: www.menopause.org.au
- The Endocrine Society: www.endo-society.org
- International Menopause Society: www.imsociety.org.

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Conflict of interest: none declared.

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