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THE PEER REVIEWED JOURNAL OF CLINICAL PRACTICE

FOREWORD FROM THE COLLECTION EDITOR

Menopause, a woman's final menstrual period, is the marker of the beginning of the second half of her adult life. It is very important for women to be as healthy and active as possible to live into old age.

Most women reach menopause between the expected ages of 48 to 53 years; however, for some women, menopause may be unexpected (premature or early menopause) or a consequence of cancer treatment or surgery with removal of the ovaries.

Menopause symptoms occur in about 75% of women, with 20% enduring symptoms that reduce their quality of life and ability to function normally. For many women, symptoms may start in the perimenopause, a time of vulnerability, with mood symptoms, including depression and tiredness; reduced coping capacity; menstrual problems; and coinciding with family and life stresses. In most women, vasomotor symptoms settle with time but the genitourinary symptoms may continue lifelong.

Menopausal hormone therapy (MHT) is the mainstay of menopause symptom treatment and is prescribed for as long as needed, with regular monitoring of duration and dosage. Nonhormonal therapies are available for women with contraindications to MHT.

This *Menopausal health* collection brings together all these aspects of management of the woman around menopause, to enable her to be fit, healthy and functioning at her desired capacity.

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Gynaecologist and Medical Director of Jean Hailes for Women's Health

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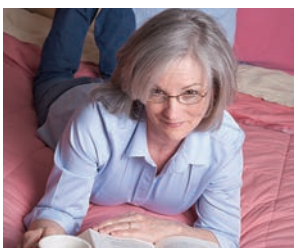

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Menopausal hormone therapy

Tips and pitfalls

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Most women experience menopausal symptoms at midlife. Healthy ageing in women should involve identifying those who would benefit from menopausal hormone therapy to improve quality of life and long-term health outcomes.

There appears to be a resurgent interest in healthy ageing in women, evident in an increasing body of lay media stories, and announcements of government funding towards menopause services. Menopause, or the permanent cessation of ovarian function, occurs naturally in most women at around the age of 51 years, and 75% of women experience menopausal symptoms. These symptoms are due to a declining level of serum estradiol, which also contributes to long-term adverse health sequelae seen in post-menopausal women. With the average female born in Australia today expected to live beyond 85 years of age, the need to optimise the health and quality of life of women as they age is compelling.[1]

This article reviews the use of menopausal hormone therapy (MHT), including the indications and options for prescription and potential risks of use, in healthy symptomatic women. It does not discuss MHT use in premature ovarian insufficiency, conservative measures and nonhormonal options for menopause treatment, as these are beyond the scope of the article.

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What is menopause and what are the symptoms?

Menopause is defined as a woman's final menstrual period, and is a retrospective diagnosis, usually based on signs and symptoms, which can only be determined after twelve months of amenorrhoea.[2] Although the menopause is usually a clinical diagnosis, for women in whom premature ovarian insufficiency (also known as premature menopause) is suspected, supportive tests to confirm the diagnosis and to rule out other aetiologies, such as pituitary disease, particularly

hyperprolactinaemia (which does not always present with galactorrhoea), include antral follicle count and follicle stimulating hormone, anti-Mullerian hormone and inhibin B levels.[2,3]

Globally, menopause occurs at an average age of 48.8 years, and at 51 years in a Caucasian population.[2,4] Premature menopause describes menopause that occurs before the age of 40, and investigations and formal diagnosis are required in this group of women because of the increased morbidity and mortality associated with the diagnosis. Early menopause is menopause occurring in women between the ages of 40 and 45 years. The importance of a woman's age at menopause goes beyond the consultation for review of her symptoms and consideration of MHT, as it influences health outcomes later in life.

Key points

- During menopause, 75% of women experience symptoms of oestrogen deficiency, including vasomotor menopausal and urogenital symptoms.
- Menopausal hormone therapy (MHT) is indicated for these bothersome symptoms, as well as for the prevention of bone loss, and is the most effective treatment.
- The benefits of MHT outweigh the risks for most healthy symptomatic women when initiated before the age of 60 years or within 10 years of menopause.
- There are only a few strong contraindications for the use of MHT; it is not prohibited and can be used cautiously in women with high-risk conditions under specialist supervision.
- There is no mandatory age cut-off or end-point to the prescription of MHT; rather shared decision making between the woman and clinician as to safe, effective treatment options should guide decisions on commencing or continued use.

Symptoms related to oestrogen deficiency include vasomotor menopausal symptoms (VMS), which include hot flushes, night sweats and mood disturbance, such as anxiety and depression, and urogenital symptoms, including vulvovaginal atrophy (VVA) and vaginal dryness, with related dyspareunia and sexual dysfunction.[5] Other common sequelae include sleep disturbance, arthralgia, myalgia, altered cognitive function and weight gain. It may be helpful to use a menopause score card, such as the Modified Greene Scale (available online at: menopause.org.au/images/stories/infosheets/docs/ams_symptom_score_card.pdf) or the menopause-specific quality of life (MENQOL) questionnaire (https://eprovide.mapi-trust.org/instruments/menopause-specific-quality- of-life-questionnaire) when in a consultation with a woman at midlife to identify and categorise her symptoms and determine the effect of treatment or resolution of symptoms in follow-up appointments.

Oestrogen deficiency is associated with long-term adverse health effects, including bone loss, increased fracture risk and cardiometabolic disease. Although weight gain cannot be specifically attributed to the menopause transition, an increase in total body adipose tissue and in central adiposity which, together with adverse lipid effects and impaired endothelial function, are seen in postmenopausal women and contribute to an increasing risk of cardiovascular disease, type 2 diabetes mellitus and certain cancers at midlife.[5-7]

When to consider treatment of menopausal symptoms

Most women experience menopausal symptoms; one in two have moderate to severe VMS, and more than one in four report moderate to severe symptoms of VVA.[8] Despite this, only a small number

1. Indications for menopausal hormone therapy

Vasomotor menopausal symptoms (VMS)

- VMS are experienced by about 75% of women, with 28.5% having moderate to severe symptoms[10]
- Symptoms tend to resolve spontaneously over time; however, many women experience symptoms for more than a decade and almost 10% of women experience bothersome VMS after the age of 60 years[11]
- Evidence shows that menopausal hormone therapy (MHT) relieves VMS and is considered first-line therapy for the relief of moderate to severe VMS[12,13]

Urogenital symptoms

- Symptoms of vulvovaginal atrophy (VVA) are experienced by 50% of women; however, only about 25% of postmenopausal women in the Western world seek medical help[14]
- The prevalence of symptoms increases with age, and they tend to progressively worsen[14]
- MHT is effective in treating moderate to severe symptoms of VVA and dyspareunia due to loss of oestrogen and, if these are the only indication for MHT, local vaginal therapy is the preferred first-line treatment[12,15]

Prevention of bone loss

- Net bone loss is seen at around two years before the final menstrual period and peaks two years after menopause[16]
- Systemic MHT has been shown to reduce the risk of bone loss and fracture similarly to other antiresorptive agents; however, its use solely for this indication is limited in Australia to women who are intolerant of, or have contraindications for, other nonhormonal bone sparing agents[2,17,18]

2. Relative contraindications for menopausal hormone therapy (MHT)

Strong contraindications

- Undiagnosed vaginal bleeding
- Oestrogen-dependent malignancy
- Active venous thromboembolic disease*†
- Severe liver disease
- Acute cardiovascular event
- Porphyria cutanea tarda

Use MHT with caution

- High risk of breast cancer
- Migraine with aura†
- Age over 65 years and no previous MHT use
- Diabetes mellitus
- Gallbladder disease†
- Hypertriglyceridaemia†
- Hepatobiliary disease†
- Past stroke or transient ischaemic attack†
- Past myocardial infarction†

* Can consider MHT use if the patient is taking anticoagulation therapy.
† Use caution in prescribing oral oestrogens.

Adapted from Davis SR, Baber RJ. Nat Rev Endocrinol 2022.[4]

receive MHT for bothersome symptoms. Misinterpretation of initial data from the 2002 Women's Health Initiative (WHI) trials determined that the overall risks of MHT outweighed the benefits and resulted in a drastic reduction in MHT prescriptions because of fears of adverse outcomes, including increased risk of coronary heart disease and invasive breast cancer.[4,9] Further research and subsequent analyses of the WHI data have informed medical practitioners and the public on the safe use of MHT. Nevertheless, careful consideration of the risks and benefits of MHT for each individual woman is key to shared decision-making about whether to initiate or continue it as a treatment option.

Indications for MHT include vasomotor symptoms, urogenital symptoms and preventing bone loss (Box 1).[10-18] Although alleviating troublesome vasomotor symptoms remains the major indication for prescribing MHT, studies have shown improvements in other symptoms of menopause including sleep, mood changes, central adiposity and joint pain and stiffness.

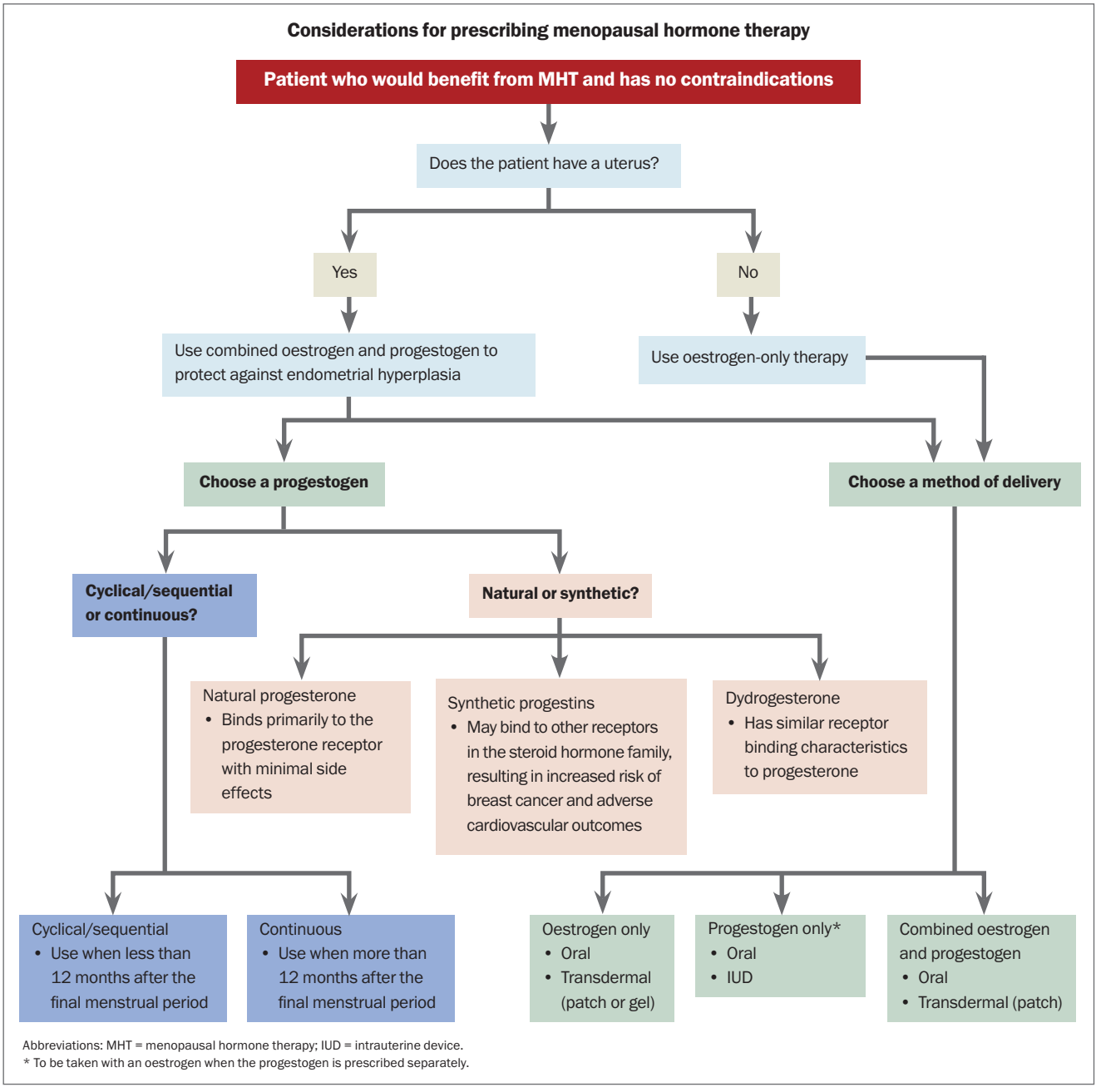
Prescribing MHT

Once it is established that a woman would benefit from MHT and she has no contraindications to its use (Box 2), it is important to consider which hormones are most appropriate for each individual patient and the best method of delivery before prescribing treatment.

Considerations for prescribing MHT are outlined in the Flowchart. For women without a uterus (i.e. who have had a hysterectomy), oestrogen-only therapy is appropriate. Women with an intact uterus must be prescribed a progestogen alongside an oestrogen to protect against endometrial hyperplasia. This can be achieved by choosing a fixed combination preparation or by prescribing an oestrogen and a progestogen separately. Progestogens are usually prescribed orally; however, the 52 mg levonorgestrel intrauterine system (IUS) is approved for use as a component of MHT for up to five years. Such approval does not apply to the lower dose 19.5 mg IUS.[19]

Estradiol may be delivered orally or transdermally. Transdermal administration is associated with a lower risk of thromboembolic disease and a more stable distribution of serum estradiol. Thus, transdermal therapy may be preferred for women who are older, at increased cardiovascular or thromboembolic risk, or who suffer from migraine headaches and mood disturbances. For some women, oral therapy is their preferred therapy choice, whereas for others, such as those who may not tolerate or respond to transdermal therapy, it may be the better option. Local vaginal oestrogen therapy is the preferred first-line treatment for women in whom VVA and dyspareunia are the only menopausal symptoms.

Cyclical/sequential oestrogen and progesterone is usually recommended for women who are within 12 months of their last menstrual period and results in a regular withdrawal bleed that should occur around the end of the progestogen phase of the cycle. Continuous combined MHT is usually prescribed for postmenopausal women and is often associated with unplanned bleeding or spotting during the first six months of therapy, after which any bleeding must be investigated.



When selecting a progestogen, it is important to consider whether a natural or synthetic product is more suitable for the woman. Progestogens bind to progesterone receptors and include:

- the natural hormone progesterone, which binds primarily to the progesterone receptor with minimal side effects
- synthetic progestins, which may bind to other receptors in the steroid hormone family to induce both desirable and undesirable side effects, and include norethisterone acetate, levonorgestrel, medroxyprogesterone acetate and drospirenone
- dydrogesterone (retroprogesterone), a retro isomer of progesterone with similar receptor-binding characteristics to progesterone.

Current international guidelines recommend the use of micronised progesterone or dydrogesterone over synthetic progestins in MHT where possible, in combination with oestrogen, to minimise adverse cardiovascular and breast effects.[2]

Tibolone is a synthetic steroid classified as a selective tissue oestrogenic activity regulator which has oestrogenic, progestogenic and androgenic effects. Tibolone is taken orally and can cause irregular bleeding if commenced earlier than 12 months after the

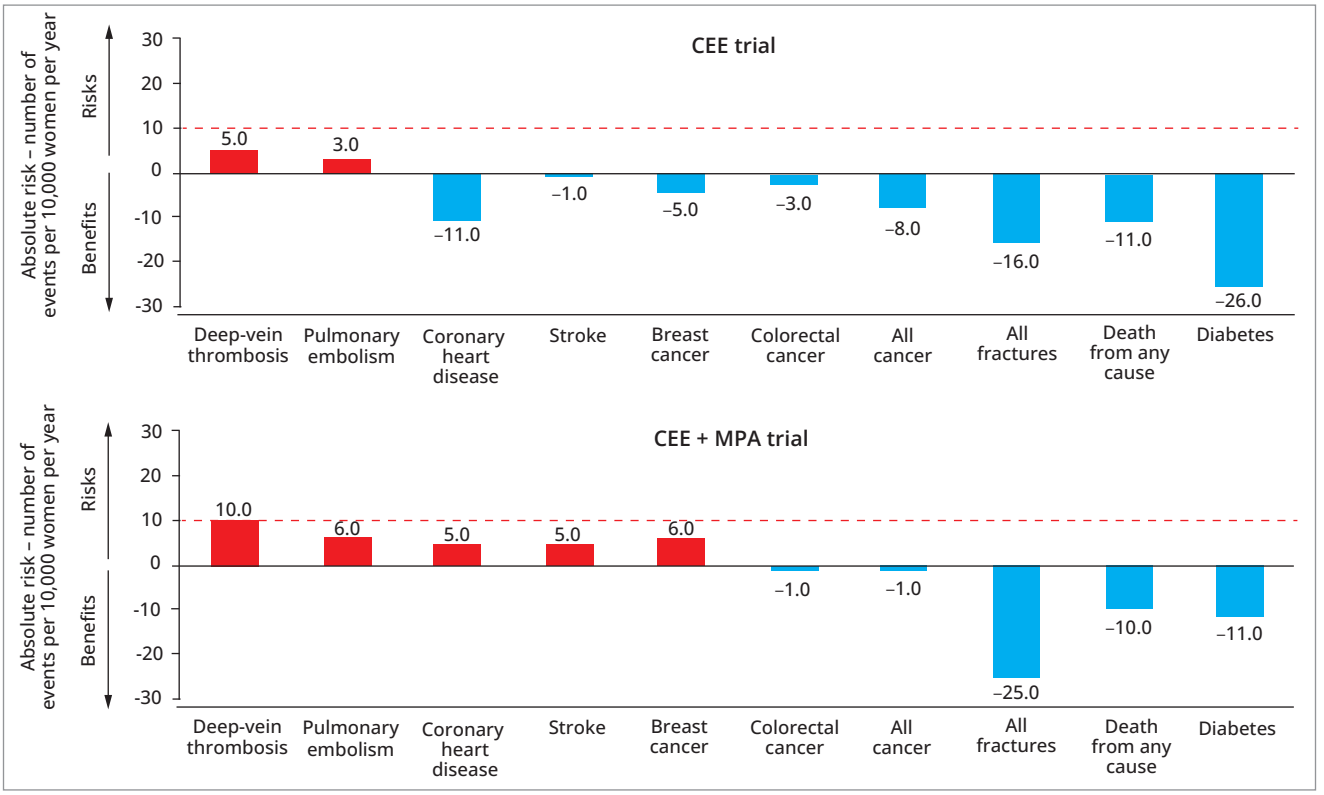


Figure. Benefits and risks of CEE alone or in combination with MPA, evaluated in the WHI study for women aged 50 to 59 years. Risks and benefits are expressed as the difference in number of events per 10,000 women per year, with less than 10 per 10,000 per year representing a rare event (dashed red line).

Adapted from Manson JE, et al. JAMA 2013.[17]

Abbreviations: CEE = conjugated equine estrogen; MPA = medroxyprogesterone acetate; WHI = Women's Health Initiative.

last menstrual period. It should therefore only be used in women who have had a hysterectomy or after 12 months of amenorrhoea.[4] Tissue selective estrogen complex is a new class of agent that combines conjugated estrogens 0.45 mg and bazedoxifene 20 mg and is taken orally; however, it is not currently available in Australia.

Hormone therapy should be commenced at a low dose and uptitrated to relieve symptoms. An exception to this advice is for women with primary ovarian insufficiency, who should be started on a standard bone-sparing dose (e.g. 2 mg estradiol, 50 mcg patch) and who may need higher doses to achieve complete relief of symptoms and bone protection. When considering dosage, clinicians and women must acknowledge the principle of using the lowest effective dose of MHT to mitigate risks. Care should include periodic re-evaluation at least every year to review the benefits and risks of continuing therapy.[12]

MHT is not contraceptive and contraception is recommended for two years after the final menstrual period for women aged under 50 years and for one year for those aged over 50 years.[19] Appropriate contraceptive options include barriers (important for safe sex), intrauterine devices and permanent measures such as bilateral salpingectomy. The combined oral contraceptive pill remains an option for perimenopausal women, unless contraindicated.

What are the risks of MHT?

Shared decision making with women and discussing risks and benefits is key when initiating and continuing MHT.[12] Before initiating MHT, women should be screened for cardiovascular and breast cancer risk, along with a thorough medical history and examination focused on elucidating any potential contraindications.[20]

The North American Menopause Society position statement on hormone therapy, published earlier in 2022, summarises the potential risks for women aged younger than 60 years, including:[12]

- breast cancer – rare with combined oestrogen and progesterone therapy
- endometrial hyperplasia and endometrial cancer – only occurs with inadequately opposed oestrogen
- venous thromboembolism – with oral oestrogen therapy
- gallbladder disease, particularly with oral oestrogens.

The absolute risk of these conditions is considered rare. Follow up from the WHI study looked at the risk of several conditions in women aged 50 to 59 years using conjugated equine estrogen (CEE) alone or in combination with medroxyprogesterone acetate (MPA) (Figure).[12,17] In patients using combined CEE and MPA therapy, there were six additional cases of breast cancer per 10,000 women compared with non-users.[17] Similarly, an additional 10 cases of deep

vein thrombosis and six cases of pulmonary embolism occurred among those using combined therapy. Risks for adverse events appear lower for oestrogen-only therapy and when a natural progestogen (rather than a synthetic such as MPA) was used for combined therapy.

Bleeding on MHT

In women with an intact uterus, unopposed oestrogens are known to increase the risk of endometrial hyperplasia and cancer. This is prevented by the addition of an appropriate dose of progestogen.[21] Women using sequential oestrogen–progestogen therapy should bleed towards the end of the progestogen phase of their regimen. Bleeding that is out of cycle, prolonged or heavier than expected requires investigation. Women commenced on continuous combined MHT may experience some unexpected bleeding or spotting during the first six months of therapy and any bleeding beyond this should also be investigated.

Appropriate investigations include taking a history, examination, transvaginal ultrasound scan to assess endometrial thickness and, if the endometrium is not clearly seen on ultrasound or is more than 5 mm thick, tissue sampling.[22] Among women who continue to bleed on continuous combined MHT in the presence of a thin endometrium, a hysteroscopy and biopsy are indicated to exclude the possibility of type 2 endometrial cancer. If results from investigations are normal, changing the MHT dose or delivery method can be considered.

When should MHT be stopped?

International guidelines do not support a mandatory limitation on the duration of MHT use.[4,12] MHT offers maximum benefits and minimum risks in healthy symptomatic postmenopausal women when it is initiated within 10 years of the last menstrual period or between the ages of 50 and 59 years. This benefit to risk ratio is lower in women who initiate MHT after the age of 60 years or more than 10 years from their last menstrual period. At annual review, an assessment of the need to continue therapy is based on the persistence of recognised indications, such as VMS and the level of bone loss, combined with evaluation of individual risk factors. Conversion from oral to transdermal delivery and possible dose reduction should be considered as age increases.

Conclusion

Most women experience menopausal symptoms at midlife, with a large proportion reporting that these symptoms are bothersome. MHT is the most effective treatment for bothersome symptoms, with few risks and compelling evidence for short- and long-term physical and psychological health benefits. Shared decision-making that takes into account the risks and benefits for each woman as well as personal preference is essential to achieve the best treatment outcomes. **ET**

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Depression

A major challenge of the menopause transition

JAYASHRI KULKARNI AM, MB BS, MPM, PhD, FRANZCP, FAHMS

Women are more likely to develop depressive symptoms during the perimenopause compared with other periods of their life, including women with no previous history of depression. Guidelines recommend antidepressant medications as first-line treatment; however, emerging evidence suggests menopausal hormone treatment may also be effective. A biopsychosocial approach to management, including treating depressive symptoms and addressing relevant psychological and lifestyle factors, offers the best outcomes and improvement in quality of life.

Depressive symptoms are common in women aged in their mid 40s to early 50s. Women at midlife (45 to 54 years of age) have the highest rates of recurrent depression of all women, and women with no previous history of depression in this age group are two to four times more likely to experience depression in the menopause transition compared with younger and older women.[1-4] Women in this important middle part of life face a number of challenges that have major psychological impacts, including concerns about ageing, dealing with workplace issues, being parents of adolescents, caring for elderly relatives and interpersonal challenges in their intimate relationships. However, in women at midlife, another important factor in the development of first-time depression or exacerbation of previous depression is the onset of menopause. Although most women do not experience significant mental ill health during the transition to menopause, an estimated 20% of perimenopausal women present to their primary health physician with depressive symptoms that may not be recognised as specifically related to menopause.[5]

Often, depressive symptoms experienced in the menopause transition are of a greater severity compared with before and after menopause.[6] Importantly, and not coincidentally, suicide rates for women in the US were highest among those aged 45 to 64 years in both 2000 (6.2 per 100,000 women) and 2016 (9.9 per 100,000).[7] Similarly, the highest completed suicide rates in women in Australia in 2021 were in those aged 45 to 49 years.[8] Therefore, it is important for clinicians to understand, recognise and manage the different types of depression that can occur in women at midlife, and which may well be due to menopausal changes. Psychiatric hospitalisation may be needed for women whose depressive symptoms, especially suicidality, have become persistent and overwhelming.

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Menopausal transition

The perimenopause marks the transition from a woman's reproductive stage to menopause. Usually occurring between the ages of 42 and 52 years, perimenopause is determined clinically by the onset of irregular menstrual cycles or variable cycle lengths. According to the Stages of Reproductive Age Workshop (STRAW), cycle lengths must differ by at least seven days and, after a woman has had one year without a menstrual period, she has completed the transition into menopause.[9] In addition to numerous somatic symptoms, one in three women will experience significant psychological changes during the transition into menopause.[4]

Studies show that women, including those with no previous history of depression, are more likely to develop depressive symptoms during the perimenopause compared with other periods of their life.[4,10,11] It has been reported that hot flushes accentuate the risk of depressive symptoms in perimenopause;[4,12] however,

KEY POINTS

- The onset of menopause can trigger symptoms of depression in women at midlife, including recurrent and new-onset depression.
- The early association between perimenopause and the onset of depressive symptoms is often missed because of the lag between the earlier onset of symptoms of depression, anxiety and cognitive changes in perimenopause and the later onset of more obvious vasomotor symptoms.
- Routine gonadal hormone peripheral blood tests do not measure the brain fluctuations in hormones – hence blood tests do not assist in the diagnosis of menopausal depression.
- Careful history taking, including for risk factors for menopause-related depression, and assessment should be done to rule out other causes of depressive symptoms.
- A woman's subjective assessment of her symptoms should be taken into consideration, particularly observations of a sudden change in mental health with no clear precipitating factors in her environment.
- Although traditional antidepressants are the recommended first-line treatment for depression in perimenopause, menopausal hormone treatment may also be effective alone or in combination with antidepressants.
- A biopsychosocial approach to management that incorporates tailored pharmacological treatments alongside lifestyle changes optimises outcomes.

many high quality studies have shown an increased risk of having depression in the menopausal transition, even when controlled for hot flushes and life stressors.[13,14] There is now crucial evidence showing that in menopause, the major gonadal hormone fluctuations impact higher brain functions, resulting in depression and related anxiety as well as cognitive changes in women who are particularly sensitive to the impact of hormone fluctuations.[15,16]

Neurobiology of menopausal depression

The neurobiology of depression is not fully understood but is thought, at least in part, to involve dopamine-serotonin pathways, with many dopamine pathways modulated by serotonergic neurons.[17] Models of depression involve altered mesolimbic signalling and dysfunction of amygdala circuits involved in emotional control.[18,19] Symptoms of depression are reversed with medications that increase dopaminergic and serotonergic transmission, indicating that depression is associated with a decline in serotonin and dopamine.[20,21]

Oestrogen has been shown to impact serotonin transmission by modulating serotonin receptor expression.[22] Oestrogen levels fluctuate during menopause, particularly the perimenopause, causing destabilising effects on mood, possibly due to changes in serotonergic neurotransmission.[23,24] Changes in transmission of other major neuropeptides, such as dehydroepiandrosterone sulphate (DHEAS) and gamma-aminobutyric acid (GABA), may be associated with depression in menopause. Levels of DHEAS decline with age, and a relationship between lower levels of DHEAS in older women and increasing symptoms of depression has been described.[15,25] Similarly, a decline in GABAergic inhibitory function is seen in postmenopausal depression and parallels the reduced levels of GABA described in major depression models.[26,27]

Regardless of the downstream neurobiological changes in the key neurotransmitter systems seen in depression, the role of oestrogen as a neuroprotective agent is important, since it appears that the fluctuation and decline in brain oestrogen levels are a crucial factor in the development of menopausal depression.

Oestrogen affects brain function

Oestrogen continually contributes to brain growth and development by regulating cell survival, differentiation, proliferation and migration, and is ultimately involved in neurogenesis.[22,28,29] Oestrogen is essential to maintaining growth factors, with oestrogen decline associated with reduced levels of brain-derived neurotropic factor.[30] Animal and human studies have shown that oestrogen improves the activity of neuronal antioxidants, thereby protecting against neurodegenerative diseases.[22,31,32] Oestrogen also affects glucose metabolism in the brain by augmenting glucose transporters, which enables better glucose utilisation, a process

paramount to neuronal homeostasis.[33,34] Moreover, estradiol-treated patients have reduced hippocampal atrophy, preserved age-related loss of grey matter and improved cerebral blood flow.[35-37]

Overall, the positive effects of oestrogen on brain structure, function and integrity – independent of age – are clear, thus, menopause may be a time of higher risk for brain disorders. Women exhibit increasing rates of amyloid deposition, accelerated hippocampal volume loss and reduced glucose utilisation across the menopausal transition, particularly within the early stage of perimenopause to menopause.[16,38]

Neuroscience provides some basis for understanding the significant impact of menopausal gonadal hormone fluctuations in the central nervous system and subsequent development of depression and related mental illness. A wealth of data from animal and clinical studies show broad beneficial effects of oestrogen administration for the brain, and hence mental health.

Diagnosing menopause-related depression is difficult

Despite growing evidence that menopausal gonadal hormone fluctuations impact the brain and subsequent development of depression and related mental illness, the use of gonadal hormone therapy in mental illness is rare and, to date, seen as experimental. This is in part due to the difficulty in recognising and diagnosing menopause-related depression. There are several reasons for this.

- Women often experience symptoms of depression and associated anxiety and cognitive changes in early perimenopause, well before the easy-to-recognise vasomotor symptoms. Therefore, the link between perimenopause and the onset of depressive symptoms is often missed.
- Menopause-related hormone changes are often missed as a key factor for depressive symptoms among the other psychosocial challenges that many women in their mid 40s face.
- There is no specific test to detect menopausal depression. Routine blood tests are unable to detect the fluctuations in central nervous system oestrogens and precursors and their impact on brain chemistry. As a result, normal hormone levels are seen in perimenopausal or postmenopausal women with depression.[39] Peripheral blood tests of the hypothalamic-pituitary-gonadal axis show changes in late transition to menopause – when clinical vasomotor symptoms are already obvious.

The current staging of menopause does not address the onset of mental health changes as the first symptoms of perimenopause in most women.[40]

Symptoms of menopause-related depression fluctuate

There appear to be two groups of women with menopause-related depression. The first is women with relapse depression, in whom previously treated depression re-presents, often with new added symptoms, and does not respond to previous or standard antidepressant treatments. The second group is de novo depression in women with no history of mental illness.

Some distinguishing features of menopause-related depression can be ascertained on clinical interviewing. Women in their mid-40s are well aware of their 'usual' stresses and coping styles, therefore, their subjective assessment of and views on their symptoms are crucial. Clinicians should take note of a woman's observations of a sudden change in her mental health with no clear precipitating factors in her environment.

It is not unusual for a woman to be profoundly depressed for days, then feel totally well for a week, only to plunge back into depression. This is due to the underlying fluctuations in the hypothalamic-pituitary-gonadal axis hormones, resulting in the fluctuating nature of menopausal depression. This is not bipolar disorder and it is important to resist this diagnosis, as such a diagnosis is usually followed by the prescription of many mood stabilisers and antipsychotics – which create unwanted physical and mental side effects.

To aid the clinician, a validated questionnaire called the 'MENO- D' has been developed for use in any clinical practice setting.[41] Specific symptoms to look for in early menopause are summarised in the Table.

Risk factors for developing menopause-related depression

Some women appear to be at greater risk of developing menopause-related depression. It is helpful to consider these risk factors as part of a clinical history and assessment of women with menopause hormone fluctuations, to delineate if symptoms are a part of the aetiology. Hormonal factors that appear to predispose women for menopause-related depression include:

- a history of premenstrual dysphoric disorder (PMDD)
- a history of depressive response to hormone contraceptives
- a history of depressive response to fertility hormone treatments
- a history of early and later life emotional, physical or sexual trauma, which create changes in the hypothalamic-pituitary-adrenal axis[42]
- severe vasomotor symptoms
- recent cessation of hormone contraception, especially if it has been taken for more than five years
- use of prolactin-elevating medications (e.g. some antipsychotics).

Perpetuating factors for any depressive disorder include past mental health problems (especially depression), excessive alcohol use, illicit drug use, poor diet, little or no exercise, poor physical health, poor support from friends and family, financial stressors, a high burden of care for others and workplace stresses.[43]

Investigations for menopause-related depression

After taking a clinical history (perhaps using the MENO- D questionnaire) and

TABLE. SPECIFIC EARLY MENOPAUSAL SYMPTOMS*

Symptom	Explanation
Low energy	Despite reasonable sleep at night, many women describe constant exhaustion
Paranoid thinking	This is of a different quality from the true delusional paranoia seen in psychosis. Common paranoid ideation includes thoughts such as 'I'm sure they are all talking behind my back about how hopeless I am at my job'
Irritability	This is a 'depressive equivalent' symptom, when instead of being sad, the woman can express anger by 'snapping', have verbal outbursts over minor incidents or even have rage responses. Importantly, the irritability is usually 'out of character' for the woman
Decreased self esteem	This can compound previous poor self-esteem issues and can present with marked self-denigratory comments. In its worst form, the woman can have no self-worth at all to the point of believing that the world would be better off without her, which can lead to suicide
Isolation	Social and occupational withdrawal, feeling isolated, 'in a bubble' even when with others
Anxiety	Heightened anxiety when doing routine and familiar tasks, or panic attacks
Somatic symptoms	Frequent headaches, muscle and joint pains limiting activity or severe aches and pains requiring pain relief and preventing activity
Sleep disturbance	Waking up several times per night due to hot flushes and sweating, plus difficulty returning to sleep
Weight	Continuing weight gain and abdominal fat deposition despite dietary restriction and increased exercise, or major weight gain (more than 6 kg) with abdominal, breast, hip and thigh fat deposition
Decreased sexual interest	Decreased libido and discomfort with sexual activity
Memory	Impaired memory leading to dysfunction
Concentration	Problems concentrating on reading, watching TV/films and work tasks

* Adapted from: Kulkarni J, et al. Transl Psychiatry 2018.[41] Available online at: https://www.maprc.org.au/sites/www.maprc.org.au/files/MENO-D_0.pdf.

performing both a physical and mental state examination, it is important to consider the following relevant investigations to support or rule out a diagnosis of menopausal depression.

- An important differential diagnosis is hypothyroidism; therefore, thyroid function tests should be performed to confirm or rule this out.[44] It is important to continue to monitor patients for hypothyroidism because thyroid disease is an independent risk factor for depression in menopausal women.
- Tests to rule out anaemia and vitamin D and B12 deficiency, which are associated with depressive symptoms.

Other investigations relevant to all menopausal women include the following.

- A dual-energy x-ray absorptiometry scan is indicated as an important health measure to evaluate bone mineral density in postmenopausal women.[44]
- Since the risk of cardiovascular disease rises after menopause, an ECG and blood lipids profile are useful baseline tests.
- A mammogram and breast ultrasound should be considered for women aged 50 years and over. Women aged under 50 years may have a breast ultrasound if hormone treatment is being considered.
- Cervical screening tests need to be tailored to the woman's age, human papillomavirus vaccination status and previous test results.[45]
- Although current guidelines do not recommend routine measurement of follicle-stimulating hormone (FSH) and luteinising hormone levels to assess menopausal status of women within the expected age range of the menopause transition, they can be measured under special circumstances, such as if menopause staging is needed. An FSH level higher than 40 IU/L can be used as a marker of final menopausal changes.[40]

It is important to remember that a woman may begin to notice changes in her mental state well before laboratory values reflect the changes and it is crucial that her observations are considered when planning treatment options.

Managing menopause-related depression

A holistic (biopsychosocial) and tailored approach that includes pharmacological treatments as well as lifestyle

modifications is important to managing patients with mental health conditions. In treating menopause-related depression, input from a multidisciplinary team, including primary health physicians, gynaecologists, endocrinologists, psychologists and psychiatrists, may be needed to optimise outcomes for each woman.

Antidepressants and perimenopausal depression

Current guidelines recommend antidepressant medications, psychological therapy and lifestyle changes as first-line management for depression during menopause.[18,46] These are not necessarily the best first-line treatments; rather, the recommendations reflect the paucity of clinical trials for hormone treatment in menopausal depression.

Antidepressants may not be efficacious for every woman, and many women describe a sense of increased emotional numbing when taking certain antidepressants and find this impairs their sense of living life fully.[47] It is therefore important to tailor the choice of antidepressant for each woman. Commercially available pharmacogenomic testing can assist clinicians to choose an appropriate antidepressant and dose. Selective serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitors (SNRIs) are generally safe and effective but can have associated adverse effects such as serotonin syndrome, agitation, nausea, diarrhoea, anorexia, excessive sweating, decreased libido or anorgasmia, headache, insomnia and akathisia. Some postmenopausal women with major depressive disorder may not respond to the widely used SSRI escitalopram, and it is possible for older women to develop tachyphylaxis to SSRIs.[19,48] Fluoxetine can have an agitating side effect and women with prominent insomnia, irritability and anxiety may report an exacerbation of these symptoms with fluoxetine treatment.[49]

The SNRI desvenlafaxine is the only antidepressant that has been studied for the treatment of perimenopausal depression in participants with clearly defined menopausal status. The randomised placebo-controlled study found that desvenlafaxine 50 mg daily was significantly efficacious in treating major depressive disorder in perimenopausal and postmenopausal women.[50]

Agomelatine is a newer antidepressant that has been shown to be effective in treating perimenopausal depression with minimal side effects.[51] A particular advantage is in the positive impact that agomelatine treatment has on insomnia, which troubles many perimenopausal women.

Psychosocial treatment

Psychotherapy is an important intervention for women with perimenopausal depression that is clearly related to employment or relationship issues. A psychologist or GP with mental health expertise can provide required supportive or exploratory therapy. Other useful psychosocial approaches include discussions about regular exercise, mindfulness techniques, yoga and providing dietary advice. Be aware that many women in early transition experience increased anxiety and use readily available alcohol for self-medication. Minimising alcohol use is very important for improving mental state and reducing physical health impacts.

Menopausal hormone treatment (MHT)

Hormone therapy alone may be appropriate for middle-aged women with mild depression, without suicidality and who are able to have MHT, when the doctor is confident that symptoms are suggestive of menopausal changes. Contraindications for MHT are:

- oral oestrogen therapy in women with personal history of venous thromboembolism
- current or recent breast cancer, or other hormone-dependent cancers.

Breast cancer risk should be evaluated before MHT is prescribed. The risk of breast cancer associated with MHT in women aged over 50 years is complex, with increased risk primarily associated with the addition of a synthetic progestogen to estrogen therapy (conjugated equine estrogen [CEE] and medroxyprogesterone acetate [MPA] continuous combined therapy) and related to the duration of use.[52]

Emerging approaches for effective MHT include starting early, careful selection of patients, personalising the dose and type to the patient and prescribing a low or ultra-low dose. The choice of MHT includes oestrogens and progestogens in different types and doses. The Australian Menopause Society (AMS) provide comprehensive evidence-based practice guidelines, updated in April 2022, that should be consulted when treating patients with MHT.[53,54] It is important that MHT is part of a holistic management strategy that also includes lifestyle recommendations on diet, exercise, smoking and alcohol use for maintaining the health of women at midlife.

Currently, clinical trials of MHT in women with menopausal depression are limited. Overall, the data so far suggest that MHT is useful in treating perimenopausal but not postmenopausal depression. One large four-year study in recently postmenopausal women reported that CEE (0.45 mg/day, with cyclic progesterone), but not transdermal estradiol (0.05 mg/day, with cyclic progesterone), improved depressive symptoms when compared with placebo.[55] Another large four-month trial found no effect with CEE (0.625 mg/day, with continuous MPA).[56]

One small study in perimenopausal women showed that depression improved significantly after three weeks' treatment with transdermal estradiol (0.05 mg/day) compared with placebo.[57] Another study showed that depressive disorders were significantly more likely to remit after 12 weeks of treatment with transdermal estradiol (0.1 mg/day) compared with placebo.[58]

MHT for menopausal depression: practice suggestions

Many types of progestins and oestrogens are available for MHT. However, to

minimise the gonadal fluctuations that adversely impact on brain neurotransmitter systems, when using MHT to treat menopausal depression it is important to choose a 'nondepressive' progestin, an oestrogen that efficiently crosses the blood brain barrier and a more constant MHT regimen.

The combined oestrogen–progestogen oral contraceptive pills (COCs) are useful first-line treatments in early transition to menopause; however, many COCs are associated with increased depression.[59] It may be useful to use a 'mood-neutral' pill for early menopause and a combined estradiol and nomegestrol pill has shown some promise in improving depressive symptoms in premenstrual dysphoric disorder and early menopausal depression.[60]

As a woman progresses in her menopausal transition, the COC may not sufficiently ease her symptoms. As the next MHT for menopausal depression, tibolone is a convenient synthetic steroid with a mixed hormonal profile. It has been shown to relieve climacteric symptoms, improve libido and assist in the management of perimenopausal anxiety and mild depression.[61-64] Additionally, tibolone does not cause increased breast density but some women may experience intermenstrual bleeding with treatment.[61]

If tibolone treatment is not sufficient to ease symptoms, a next step in MHT for menopausal depression could be using a combination of a progestin and a more potent oestrogen, namely 17-beta estradiol, which effectively crosses the blood-brain barrier. There are many ways of delivering estradiol, and 50 mcg (medium dose) or 100 mcg (high dose) patches are commonly used. Pump delivery of estradiol is also a convenient delivery system. It is important not to use conjugated estrogen treatment for menopausal depression since these preparations do not cross into the brain. In addition to the estradiol, micronised oral progesterone (100 mg or 200 mg) is less depressive and can be administered as a regular regimen, even in women who have had a hysterectomy.[54]

Selective estrogen receptor modulators (SERMs) are a new class of synthetic hormones shown to have the beneficial therapeutic effects of oestrogen on bone, lipids and the brain while minimising adverse effects on the uterus and breasts.[65,66] A newer combination of the SERM bazedoxifene with conjugated estrogens has been shown to improve menopausal symptoms in healthy postmenopausal women.[67] It is commercially available for moderate to severe vasomotor symptoms associated with menopause in women with a uterus, and it has potential as a future option for treating menopausal depression; however, clinical trials with SERMs to treat depression are limited and more data on this aspect is needed.

The risks and benefits of MHT differ for women during the menopause transition compared with those for older postmenopausal women. The International Menopause Society does not recommend bioidentical hormones because of standardisation and dosing issues.[52] The International Menopause Society guidelines further recommend: 'Women taking MHT should have at least an annual consultation to include a physical examination, update of medical and family history, relevant laboratory and imaging investigations, a discussion on lifestyle, and strategies to prevent or reduce chronic disease. There is currently no indication for increased mammographic or cervical smear screening'.[52]

Combination MHT and antidepressant therapy

In menopausal women with depression who do not respond to first-line treatment with either MHT or antidepressants, both classes of treatment may be combined.[68] An optimal combination is transdermal estradiol, oral progesterone (100 mg) and an antidepressant with a low potential for agitation or emotional numbing side effects, such as agomelatine and vortioxetine. Brain stimulation techniques such as transcranial magnetic stimulation may also be efficacious in combination with MHT. In such situations, all medication and therapy adverse effects need to be monitored carefully.

Conclusion

The menopausal transition is a major biological event that all women experience. Early recognition of mental health issues related to the menopause and initiating biologically tailored treatment are essential to effective management. Most women with perimenopausal depression respond to treatment, and many current and emerging hormone treatments are available. Depression in midlife women requires a new approach with hormone treatments and appropriate antidepressant medication as well as psychological and lifestyle considerations. MT

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A list of references is included in the online version of this article (www.medicinetoday.com.au).

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Depression

A major challenge of the menopause transition

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A tailored approach to managing menopause

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When treating women around menopause, consideration of each woman's reproductive status and subsequent effects to her health, as well as clinical history and assessment findings, is important. Lifestyle changes are first-line approaches to management, regardless of menopausal status. Menopausal hormone therapy (MHT) is effective in managing menopause symptoms in women, but GPs should be aware of the risks of long-term use and manage patients accordingly. Women in whom MHT is contraindicated should be offered nonhormonal therapy.

Menopause is a clinical diagnosis in older women, defined by an absence of menstrual periods for 12 consecutive months. After this, women are considered postmenopausal. In young women who experience amenorrhoea, premature ovarian insufficiency should be considered a possible diagnosis for her symptoms, and biochemical assessment is needed to confirm a diagnosis.

Perimenopause is defined from the onset of irregular periods until 12 months after the final menstrual period, specifically with at least a seven-day difference between cycle lengths.[1] Towards the end of the reproductive years, fertility diminishes and ovarian activity becomes erratic, leading to potential menstrual irregularity and the development of symptoms representing both low and high hormonal levels. Anovulatory cycles (i.e. absence of ovulation) become more frequent and can lead to irregular periods, increasing the risk of endometrial proliferation, hyperplasia and possible endometrial cancer. Ovulation may occur twice in a menstrual cycle, the second time being during a period (known as LOOP; luteal out of phase ovulation).[2]

Menopause management of each woman entails the development of an individualised treatment plan following assessment and investigation, primarily by an appropriate and thorough history and examination. Importantly, a woman's menopausal status influences her management; therefore, understanding the stages of menopause, associated symptoms and treatment options is important to appropriate and effective management. Using two example cases, this article highlights the importance of an individualised approach to managing women in the menopause.

Case 1. A 49-year-old woman with perimenopausal symptoms

Perimenopause is a period that may be without any disruption to a woman's quality of life, but for many women it is a time of change in wellbeing, mood and coping capacity as well as menstrual irregularity and physical symptoms. Some women will experience increasing premenstrual symptoms, heavy and/or erratic periods and abnormal bleeding. Oestrogen levels at this time may be quite high, and may cause breast tenderness, bloating, anxiety or headaches.[2] Women may also have low oestrogen levels, leading to vasomotor symptoms, including night sweats and flushes that are intermittent or regular.

Presentation

Ms A is a 49-year-old secondary teacher who is divorced with two adult children aged 21 and 23 years. She has experienced irregular periods for eight months and had a recent heavy period with clots lasting 10 days after two months of amenorrhoea. She has increasing anxiety and stress levels with less capacity to manage her life. Her sleep pattern is disturbed; she is waking up at night feeling hotter than normal and is tired.

She has a new partner and is concerned about using appropriate contraception. Her general health is good, she exercises regularly, has a good diet and is not on any medications, except for vitamin D 1000 IU per day. She is a nonsmoker and drinks alcohol rarely. There is no significant medical or surgical history

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except for the delivery of her two children by caesarean section. Her mother had morbid obesity and severe hypertension, and died at the age of 78 years of a heart attack. Her father is 82 years old and has type 2 diabetes, but is otherwise well.

General and gynaecological examination reveals her uterus is bulky, similar in size to a nine-week pregnancy. She has no other major abnormalities.

Assessment

The first steps are assessing Ms A and determining the differential diagnoses. The following issues should be considered with regard to Ms A's symptoms, history and examination:

- irregular periods
- heavy menstrual bleeding
- wakefulness
- anxiety and stress
- increased body heat
- new relationship
- contraception
- bulky uterus.

Based on Ms A's symptoms and history, a number of differential diagnoses should be considered.

- Perimenopause – her age and the symptom complex are consistent with the perimenopause.
- Endometrial hyperplasia – heavy menstrual bleeding (HMB) with clots after a few months of amenorrhoea may be associated with a thickened endometrium. Also, anovulatory cycles during the perimenopause lead to endometrial proliferation and thickening. This is of more concern in women with obesity, as testosterone is metabolised to oestrogen in peripheral fat leading to added oestrogen stimulation.
- Adenomyosis or fibroids – both can cause a bulky uterus and HMB.
- Spontaneous abortion/miscarriage – she experienced HMB after a period of amenorrhoea. She is also concerned about contraception.
- Sleep disorder – she is wakeful and tired.
- Anxiety disorder – mood disorders are common or recur in women in their 40s and 50s due to changing hormone levels.
- Thyroid dysfunction – may develop around the perimenopausal period.
- Diabetes – may cause flushing.

Investigations

Given the above differential diagnoses, the following investigations should be done:

- full blood examination
- pregnancy test
- thyroid function test
- iron studies
- fasting blood sugar level
- ultrasound transvaginal (preferably when the period is ceasing or immediately after, as the endometrium will be at its thinnest).

Hormone level tests are not routinely recommended in the perimenopause because they are very variable at this time and unlikely to assist in the diagnosis. For instance, it is possible to see estradiol levels suggestive of ovulation one week and elevated follicle stimulating hormone level the next. Occasionally, when there are no discernible cycles or a woman has had a hysterectomy, a series of hormone level tests may be required. If a diagnosis is made on a single hormone level in the perimenopause, inappropriate treatment may be prescribed.

Management

Ms A's management should start with lifestyle recommendations, including:

- eating nutritious foods
- maintaining a regular exercise program
- having regular routine screening and medical examinations, including blood pressure and breast examinations
- having a cervical screen test
- regular mammograms
- having regular screening for cardiovascular disease and bone health.

Perimenopausal irregular bleeding is common but an assessment of the endometrial thickness on ultrasound is important to determine whether Ms A requires an endometrial biopsy or hysteroscopy and curettage in order to exclude endometrial hyperplasia or carcinoma. There are a number of treatment options to manage both her irregular heavy periods and her contraceptive needs. These include the combined oral contraceptive (COC) pill or ring, the levonorgestrel-releasing intrauterine device (LNG IUD) and the 4 mg drospirenone pill. Stabilising her cycle and providing contraception may help to relieve Ms A's anxiety and stress. Prescribing estradiol-containing COCs in the perimenopause can help treat heavy and/or irregular periods, provide contraception and relieve hot flushes and sweats. They also have lesser effects on haemostasis, fibrinolysis markers, lipids and carbohydrate metabolism.[3] Although the LNG IUD provides effective contraception and reduces menstrual bleeding over time, it has no effect on vasomotor symptoms, and additional oestrogen is required with its use, usually as an estradiol patch or gel.

If all of Ms A's investigation results are normal except for the bulky uterus found on the ultrasound and examination, determine the most appropriate treatments available. Ms A should be asked to diarise her symptoms and bleeding to assess improvement and be given a copy of her treatment plan, summarised in Box 1.

Case 2. A 53-year-old woman with postmenopausal symptoms

The term menopause refers to the final menstrual period, so the diagnosis is always retrospectively made after 12 months of amenorrhoea. Once a woman is 12 months past her final menstrual period, she is postmenopausal for the rest of her life. Commonly reported symptoms include:

- vasomotor symptoms of hot flushes and sweats usually at night, with sleep disturbance
- muscle and joint aches and pains
- anxiety and irritability

1. MANAGEMENT PLAN FOR THE PERIMENOPAUSAL WOMAN PRESENTED IN CASE 1 – A SUMMARY

- Investigations
- Lifestyle recommendations as fist-line management
- Combined oral contraceptive pill or levonorgestrel-releasing intrauterine device with an estradiol preparation
- Review in two months

- decreased concentration
- loss of libido
- vaginal dryness and other genitourinary symptoms related to lack of oestrogen, including painful intercourse (dyspareunia)
- fatigue and tiredness
- crawling sensations on the skin (formication)
- reduced wellbeing and diminished quality of life.

After the menopause, women are at increased risk of developing heart disease, osteoporosis, central adiposity, genitourinary disorders and mood disorders.

Presentation

Ms B is a 53-year-old company director who presents with hot flushes, night sweats, sleep disturbance, tiredness, difficulty with word finding, reduced libido and some dyspareunia due to vaginal dryness. Her last menstrual period was at 51 years and she has had no further spotting, staining or bleeding. Her last cervical screen was 12 months ago and her mammogram is due in 2023. Her last blood test revealed her fasting cholesterol level was 6.3 mmol/L but her cholesterol/HDL ratio was normal.

Her exercise routine has suffered and her alcohol consumption increased during the COVID-19 pandemic, and she has gained weight. She stopped smoking five years ago because of regular bronchitis. Her body mass index is 29 kg/m^2 and her blood pressure is 140/90 mmHg. A history and examination reveal no other abnormalities. She lives alone and has no children, but has a partner who lives nearby. Her mother has osteoporosis and her father has had prostate cancer and hypertension, all controlled.

Her symptoms are embarrassing her, especially when she is presenting in important meetings, and her self-esteem, confidence and body image are diminished. She has tried a number of over-the-counter menopause products but none have been effective in relieving her symptoms. She wants to try menopausal hormone therapy (MHT, previously known as hormone replacement therapy [HRT]).

Investigations

Ms B should undergo general blood tests including cholesterol, glucose, thyroid, calcium and vitamin D levels and iron studies, if these have not been performed within the last 12 months. Her screening tests should also be checked to ensure these are up to date.

Assessment

Menopausal hormone therapy

In a postmenopausal woman who has not had either a premature or early menopause, the lowest effective dose of MHT is prescribed. The usual advice is to start at a low dose and increase at a later consultation if there has been inadequate symptom relief.

Within the first one to two years after the final menstrual period, sequential/cyclical MHT therapy is recommended, comprising continuous oestrogen plus progestogen for 12 to 14 days per cycle to ensure a regular bleed occurs. Most women after that time prefer continuous oestrogen–progestogen therapy to avoid further bleeding and give greater endometrial protection. If a woman has had a hysterectomy, then she requires oestrogen-only therapy, as the role of progestogen is primarily to protect the endometrium from the normal proliferation of oestrogen.

MHTs include various oestrogen–progestogen preparations, both oral and transdermal, the steroid tibolone, tissue-selective estrogen complex (TSEC) comprising a conjugated oestrogen and bazedoxifene combination, and individual oestrogen-only and progestogen-only products. An up-to-date list is available online at: www.menopause.org.au/hp/information-sheets/ams-guide-to-equivalent-mht-hrt-doses. Other resources on menopause are listed in Box 2.

2. RESOURCES FOR GPS

Jean Hailes for Women's Health:
www.jeanhailes.org.au/resources/menopause-health-professional-tool

Australasian Menopause Society:
www.menopause.org.au

Side effects from MHT are common (Box 3) but usually settle within the first few months of therapy. Breakthrough bleeding within the first six months of therapy is not considered abnormal unless it is prolonged. Any breakthrough bleeding after that time should be investigated for a cause such as an endometrial polyp.

Nonhormonal prescription therapies or referral to a menopause specialist or clinic should be recommended to women in whom MHT is contraindicated. Contraindications for MHT are listed in Box 4. Nonhormonal prescription therapies include selective serotonin reuptake inhibitors (SSRIs), selective noradrenaline reuptake inhibitor antidepressants (SNRIs), gabapentin or pregabalin (both used for chronic pain or as antiepileptic medications) and clonidine (an antihypertensive that has been used for many years). Oxybutynin (used for an overactive bladder) has also been used for vasomotor symptoms.[4] These agents have shown a reduction of vasomotor symptoms in research studies and all are used off-label for this purpose. Other therapies that have shown some reduction in vasomotor symptoms include cognitive behavioural therapy and hypnotherapy.

Risks of MHT

MHT increases the risk of breast cancer, although the level of risk depends on the therapy prescribed, the dose and duration of therapy and the age of the woman. Oestrogen-only therapy is associated with a lower risk than combined therapy. The risks are lower in women aged 50 to 59 years, and increase with ongoing use.

3. SIDE EFFECTS OF MENOPAUSAL HORMONE THERAPY

- Bloating and fluid retention
- Breast tenderness and swelling
- Nausea and indigestion
- Leg cramps
- Headaches
- Vaginal bleeding
- Mood swings or reduced mood
- Abdominal pain
- Acne, with some androgenic progestogens

4. CONTRAINDICATIONS TO MENOPAUSAL HORMONE THERAPY

MHT is contraindicated in women with a history of:

- hormone dependent cancers, including breast cancers and endometrial cancer greater than stage 1
- thrombophilias or past venous thromboembolic events
- undiagnosed vaginal bleeding
- uncontrolled hypertension
- cardiovascular disease or major risk factors for cardiovascular disease
- active liver disease

5. MANAGEMENT PLAN FOR THE POSTMENOPAUSAL WOMAN PRESENTED IN CASE 2 – A SUMMARY

- Lifestyle recommendations
- Menopausal hormone therapy – transdermal oestrogen with oral progesterone
- Vaginal oestrogen for vaginal dryness
- Review in two months

The Women's Health Initiative (WHI) study showed that the risk of breast cancer increased by eight additional breast cancer cases per 10,000 for women on oestrogen–progestin therapy for five years or more.[5] Results from two nested case-control studies showed an additional three cases per 10,000 women years for oestrogen-only therapy and nine additional cases per 10,000 women years for oestrogen–progestogen therapy in women near the menopause and up to five years' use. The risk decreased after stopping MHT.[6] However, a long-term follow up of women in the WHI study showed a reduced incidence of breast cancer in the oestrogen-only group.[7] Progestogens, progesterone and dydrogestrone have a lower risk of breast cancer compared with medroxyprogesterone acetate, norethisterone and LNG, which are associated with a higher risk.[6]

The risk of breast cancer in women with a positive family history is the same whether they are on MHT or a nonuser. The risk is increased in women with obesity but not compounded if on MHT. Importantly, there is no increased breast cancer risk for women using vaginal oestrogen-only therapy.

The risk of thromboembolism is increased by two to three per 1000 women years with oral MHT compared with one per 1000 woman years in those who do not take MHT. There is no increase in thromboembolic risk with transdermal MHT use; however, the data only included up to medium doses. Women with obesity and those who smoke have higher rates of venous thromboembolism which is increased further if they take oral MHT.[8]

Cardiovascular disease risk is not increased in women using MHT within 10 years of the menopause. It is associated with age at which MHT is commenced and increasing age. Overall, protection from heart disease and reduced mortality was seen in women prescribed MHT at 50 to 60 years of age or within 10 years of their final menstrual period.[9]

Management

As with Ms A, lifestyle recommendations are first-line management strategies. For Ms B these include:

- assessment of diet with recommendations for healthy eating
- referral to a dietitian to assess her diet if she wants to lose weight
- recommendation of an exercise program to suit her lifestyle and encouragement of daily exercise
- recommendation to reduce her alcohol consumption, which may also lead to weight loss
- check of her emotional health as she has a high-level position that requires good memory and concentration, is working from home and lives alone and was isolated during COVID-19 lockdowns.

As it has been two years since Ms B's final menstrual period, a continuous regimen of oestrogen–progestogen therapy is suitable. The risks of thrombosis are lower with a transdermal oestrogen product and progesterone use.

Vaginal oestrogen, either as a tablet, pessary or cream, is suitable to help Ms B's vaginal dryness. Inserting the oestrogen into the lower-third of the vagina is recommended because of the pudendal and perineal vessels supplying the lower pelvis, with lower levels of oestrogen absorption in the lower-third compared with the upper two-thirds.[10] A summary of Ms B's management plan is presented in Box 5.

Conclusion

Menopause treatment options vary with the phase at which a woman presents – in the perimenopause, the immediate postmenopause or some years later. Her symptom complex, past and family history and her own preferences will guide her treatment. Informing the woman of the risks and benefits enables her to decide what MHT she wishes to trial. If MHT is contraindicated, nonhormonal therapies are effective and should be offered. Above all, it is important to tailor the therapy to meet each individual woman's needs. MT

References

A list of references is included in the online version of this article (www.medicinetoday.com.au).

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A tailored approach to managing menopause

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Premature ovarian insufficiency

Not 'too young for menopause'

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Premature ovarian insufficiency, which is defined as loss of ovarian activity before the age of 40 years, has negative health impacts. Prompt diagnosis, evaluation of cause and sequelae, psychological support and institution of hormone replacement therapy are essential components of management.

Premature ovarian insufficiency (POI), also known as premature menopause or premature ovarian failure, is defined as the loss of ovarian activity before the age of 40 years.[1] It may occur spontaneously or secondary to medical treatments. Management should incorporate consideration of symptoms experienced, psychological health and desire for fertility, as well as the long-term sequelae related to bone and cardiovascular health. Hormone replacement therapy is recommended until the age of natural menopause.

Resources are available to assist with the care of women affected by POI developed by Monash Centre for Health Research and Implementation, Melbourne (MCHRI), and available online (https://mchri.org.au/guidelines-resources/health-professionals/early-menopause-practice-tools/). These include algorithms for the diagnosis and evaluation and for the management of POI, which are based on a systematic search of menopause guidelines, AGREE (Appraisal of Guidelines for Research and Evaluation) evaluation and extraction of recommendations related to POI. The algorithms are shown below. The evidence-based Ask Early Menopause app is freely available that provides quality information for women with early menopause or POI (Figure).

Terminology

The term 'menopausal hormone therapy' (MHT) is now preferred when referring to oestrogen and progestin preparations for managing menopause. However, the term 'hormone replacement therapy' (HRT) is used in this article for women with premature ovarian insufficiency (and is also used in the European Society of Human Reproduction and Embryology [ESHRE] guideline),[1] as this reflects the fact that in this setting women are using preparations to replace hormones that would normally be produced by the ovaries. In addition, some young women find the term MHT less appealing than HRT.

Case scenario

Karima is a 35-year-old woman who presents to her GP with an eight-month history of amenorrhoea, hot flushing, hair loss and loss of libido that is affecting her relationship with her husband. She and her husband have two daughters but have been hoping to have more children, particularly as in their culture a son is very much desired. Karima is a nonsmoker and does not drink alcohol. She does not take any medications and has no previous medical or surgical history.

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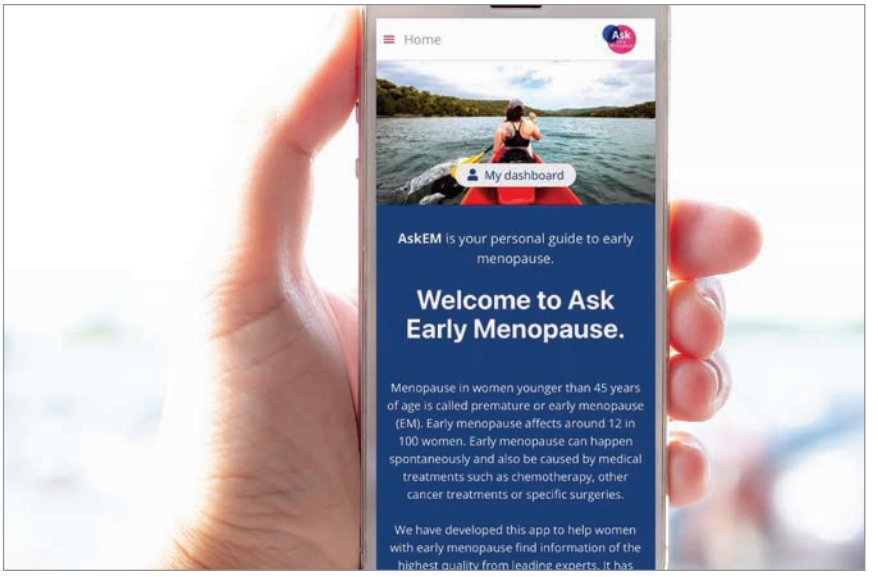

Figure. The Ask Early Menopause app provides evidence-based information for women with early menopause or POI (www.askearlymenopause.org).
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What investigations should be performed to determine the cause of Karima's secondary amenorrhoea?

Although the most common causes of secondary amenorrhoea are pregnancy, polycystic ovary syndrome and hypothalamic or pituitary disease, POI should also be considered in a young woman with oligo- or amenorrhoea. Spontaneous POI affects up to 4% of women.[2]

Diagnostic criteria for POI are oligo- or amenorrhoea for at least four months and FSH levels in the postmenopausal range (>25 IU/L) on two tests performed at least four to six weeks apart (Flowchart 1).[1,3,4] Women should not be taking hormonal medication at the time of testing. Anti-Müllerian hormone (AMH) testing is not recommended for the diagnosis of POI, although it is used by specialists for fertility assessment.[1,3]

Karima's initial investigations include a negative pregnancy test and show normal TSH and prolactin levels. Her FSH is elevated (68 IU/L and 101 IU/L) and her estradiol low (86 pmol/L and 76 pmol/L) on two occasions, six weeks apart, confirming the diagnosis of spontaneous POI.

What could be the cause of Karima's POI and what investigations should be performed?

Known causes of POI include genetic, autoimmune and infectious diseases and iatrogenic factors (Box 1). Iatrogenic POI is becoming more common with advances in cancer treatment and risk-reducing bilateral oophorectomy. The risk of iatrogenic POI depends on a patient's age, type and dose of chemotherapy, and dose and field of radiotherapy.[4] Most cases of POI are unexplained or idiopathic and may reflect gene mutations that currently are not readily detected.[6]

Chromosomal abnormalities are found in 10 to 12% of women with POI, and may cause primary or secondary amenorrhoea.[7,8] If Y chromosomal material is detected then there is an elevated risk of gonadoblastoma, and gonadectomy is usually advised.[9] Sporadic and familial fragile X *(FMR-1)* premutation has been reported in up to 7.5% and 13% of Caucasian women with POI, respectively, but it is less prevalent in Indian women and Chinese women with POI.[1,10,11] The presence of this mutation has implications for a woman's offspring and other family members. If any genetic abnormalities are detected then the woman should be referred to genetic services.

On exclusion of genetic causes, an autoimmune screen should be performed, including 21-hydroxylase antibody (21OH-Ab) or adrenocortical antibodies for adrenal autoimmunity and anti-thyroid peroxidase antibodies (TPO-Ab). If 21OH-Ab is positive, the woman should be referred to an endocrinologist for further assessment of adrenal function. If the woman is TPO-Ab positive, TSH should be measured yearly because of the increased risk of hypothyroidism secondary to Hashimoto thyroiditis.

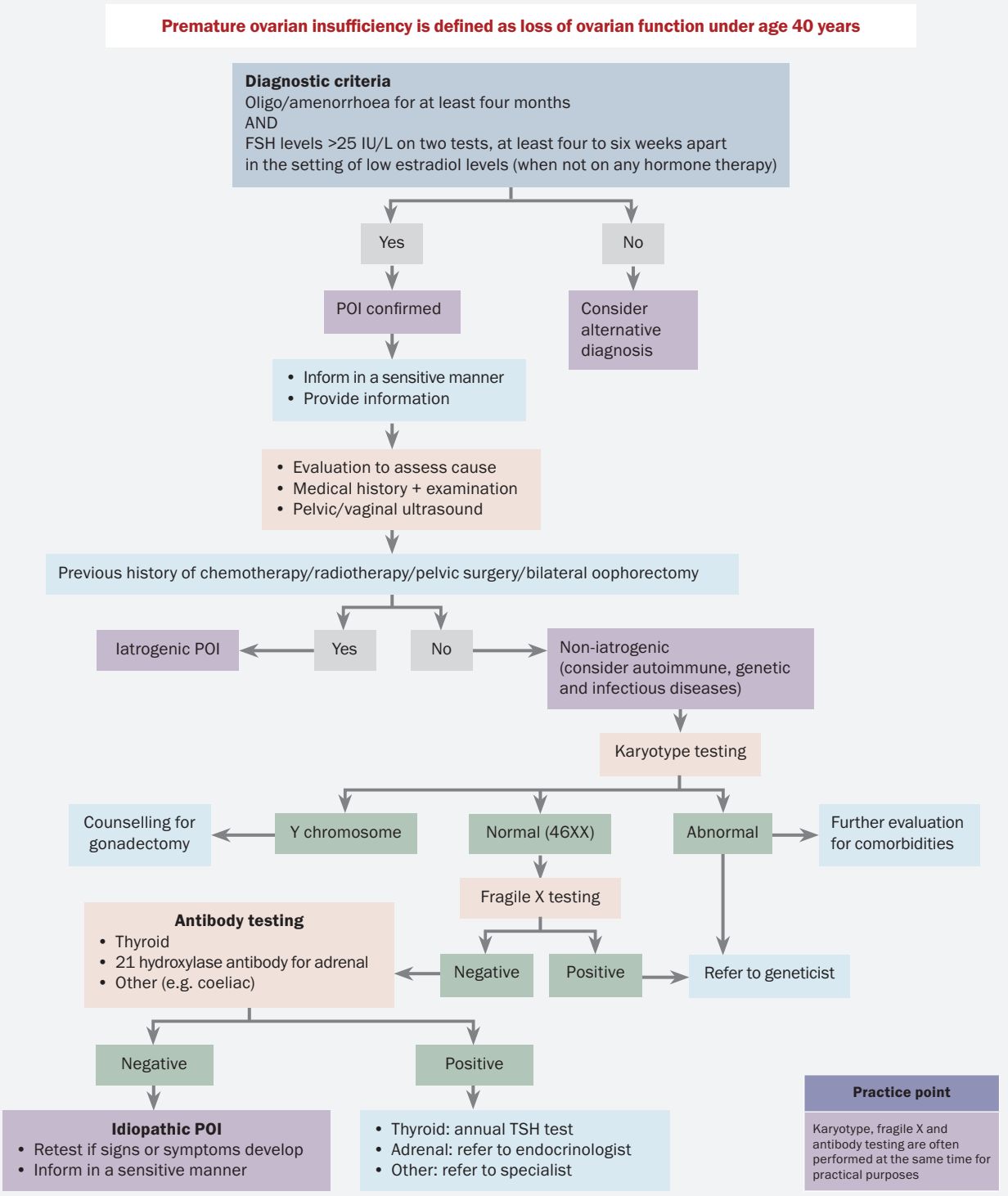
In practice, karyotype, fragile X testing and autoantibody testing may be requested at the same time. Ovarian antibody testing is nonspecific and is not recommended. Testing for other autoimmune disorders may be indicated depending on initial history and examination.

What are the initial steps in the management of Karima's symptoms and concerns?

POI can be a devastating diagnosis for many women, especially when it is unexpected and no underlying cause has been found. Early referral to psychology services and support groups (e.g. Daisy Network) may be beneficial (Flowchart 2). In addition, careful assessment for depression or anxiety is important. Lifestyle recommendations for women with POI are directed at menopausal symptom control, cardiovascular disease risk reduction and bone health. Women should be given appropriate information or referred to good quality resources – examples of useful websites are given in Box 2.

Baseline investigations are directed at determining choice of hormone replacement therapy, assessing fertility, and evaluating

1. MANAGEMENT ALGORITHM FOR DIAGNOSIS/EVALUATION OF PREMATURE OVARIAN INSUFFICIENCY (POI)



Abbreviations: FSH = follicle stimulating hormone; TSH = thyroid stimulating hormone.

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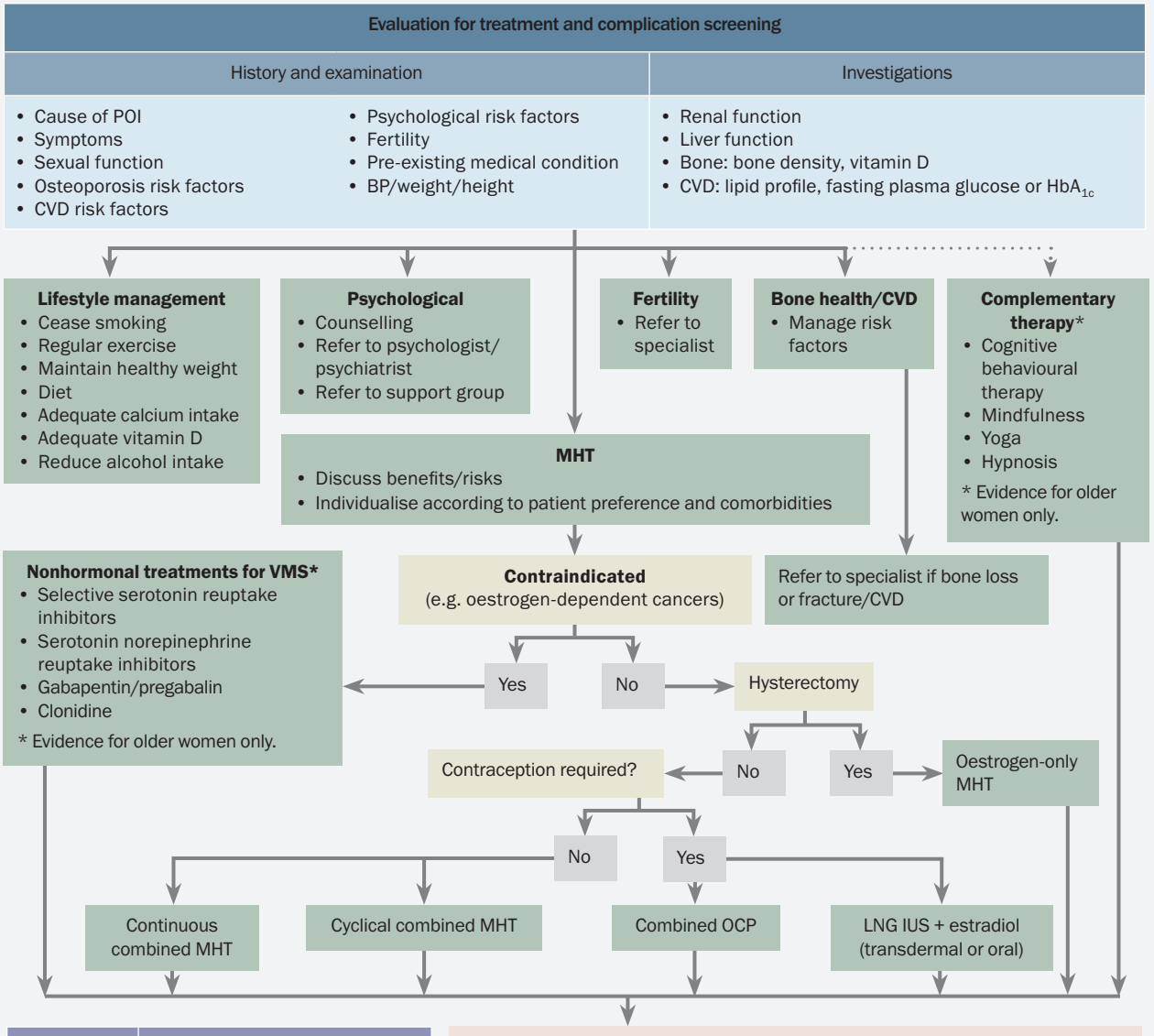
2. MANAGEMENT ALGORITHM FOR PREMATURE OVARIAN INSUFFICIENCY (POI)



Women with special issue	MHT
Breast cancer	• Contraindicated
Positive *BRCA1/2* post RR BSO	• Not contraindicated if no history of breast cancer (short-term use)
Endometriosis	• Combined MHT may reduce disease reactivation
Fibroids	• Not contraindicated
Turner syndrome	• Not contraindicated
Migraine	• Transdermal MHT is preferred
Hypertension	• Transdermal MHT is preferred • MHT may have a beneficial effect on BP compared to OCP
History of VTE	• Refer to a haematologist prior to MHT • Transdermal MHT is preferred
Obese/overweight	• Transdermal MHT is preferred

Monitoring (all women with POI)

- MHT until the age of natural menopause (unless contraindicated)
- Annual clinical review to assess MHT risks/benefits (CVD/bone health)
- Mammogram as per national recommendations
- Pap smear as per national recommendations
- Yearly thyroid stimulating hormone if positive thyroid antibody
- No specific recommendation regarding repeating antibody if initially negative

Additional notes

- Usual contraindications to OCP apply
- 17 beta-E is preferred to EE/CEE
- Higher dose may be required (e.g. transdermal E, 75 to 100µg, oral E >2mg/daily)
- Cyclical combined MHT is preferred (no longer than 12 weeks)
- Vaginal oestrogen if persisting urogenital symptoms on MHT
- Consider short-term use of testosterone patches/creams for sexual function (lack of evidence on long-term effects)
- Insufficient evidence to recommend herbal therapies/complementary medicine

Abbreviations: BP = blood pressure; CEE = conjugated equine estrogen; CVD = cardiovascular disease; E = estradiol; EE = ethinyl estradiol; LNG IUS = levonorgestrel intrauterine system; MHT = menopausal hormone therapy; OCP = oral contraceptive pill; RR BSO = risk reduction bilateral salpingo-oophorectomy; VMS = vasomotor symptoms; VTE = venous thromboembolism.

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cardiovascular and osteoporosis risk. They include renal and liver function, pelvic ultrasound, AMH level, lipid profile, fasting plasma glucose, calcium, phosphate and vitamin D measurements and bone mineral density (BMD) scanning. Cervical screening should be up to date.

When and how should hormone replacement therapy be prescribed?

Recommendations for HRT in women with POI (Flowchart 2) are derived from observational studies and small clinical trials of women with POI due to Turner syndrome, bilateral oophorectomy or chemotherapy, or idiopathic in origin, and from evidence in women experiencing menopause at the usual age. As well as being the most effective treatment for vasomotor symptoms, HRT has been shown to improve genitourinary symptoms, sleep and emotional wellbeing. HRT is also important for long-term health by reducing the risk of cardiovascular disease, cognitive dysfunction and osteoporosis.[12-14]

HRT ameliorates the impact of POI on bone health, and has beneficial effects on cardiovascular and metabolic health, including lowering blood pressure and improving endothelial function and lipid profile.[15-23] In women with Turner syndrome, HRT has been shown to improve liver function and increase lean body mass.[21,24,25] HRT is recommended for women with POI until the average age of natural menopause (51 years); however, the optimal HRT preparation is unknown. Delay in initiation of HRT is associated with lower BMD, smaller uterine size and decreased quality of life. The choice of HRT depends on the cause of POI, need for pubertal induction, need for contraception, comorbidities and patient preference. Some women may prefer a regular withdrawal bleed and thus cyclical therapy (12 to 14 days of added progestogen per month) is appropriate, whereas others may prefer no withdrawal bleeds with a continuous progestogen regimen. A cyclical regimen stimulating active functioning of the endometrium with regular proliferation and withdrawal bleeding may be preferable in women aiming for pregnancy by oocyte donation, with amenorrhoea potentially indicating pregnancy.[1]

There is evidence that physiological estradiol may confer a greater benefit for BMD compared with ethinylestradiol or conjugated estrogens.[16,19,20] Recommended doses for bone protection are at least 2 mg oral estradiol daily or 100 mcg transdermal estradiol weekly or twice weekly.[25,26] Studies in postmenopausal women of typical age indicate that micronised progesterone has advantages in regard to breast cancer and venous thromboembolism risk compared to other progestogens.[27,28] Transdermal estradiol with cyclical micronised progesterone most closely approximates 'body-identical' HRT. Tibolone and the oral combined preparation of bazedoxifene acetate and conjugated estrogens have not been studied in women with POI.

1. CAUSES OF PREMATURE OVARIAN INSUFFICIENCY

Genetic

- Chromosomal abnormalities (most commonly X structural abnormalities or X aneuploidy, including Turner syndrome)
- Fragile X syndrome (*FMR-1* premutation)
- Other autosomal gene defects (e.g. *NOBOX, GDF9, FIGLA, SOHLH1, SOHLH2, NR5A1 (SF1), FSHR 5*)

Autoimmune (associated conditions)

- Hypothyroidism
- Addison's disease
- Type 1 diabetes
- Coeliac disease
- Autoimmune polyendocrine syndrome type 1 and 2
- Immune thrombocytopenic purpura, autoimmune haemolytic anaemia, pernicious anaemia
- Vitiligo, alopecia areata
- Inflammatory bowel disease, primary biliary cirrhosis
- Systemic lupus erythematosus, rheumatoid arthritis, Sjögren's syndrome
- Glomerulonephritis
- Multiple sclerosis, myasthenia gravis

Iatrogenic

- Chemotherapy (e.g. alkylating agents)
- Abdominopelvic radiation, total body irradiation
- Bilateral oophorectomy, ovarian surgery

Other

- Mumps oophoritis
- Galactosaemia

HRT is not contraceptive. Estradiol-containing combined oral contraceptives (COCs) have not been studied in POI, although may be considered in women desiring contraception. Continuous or long cycle use of COCs is preferred for bone health, avoiding the non-oestrogen inactive tablets.[26] The levonorgestrel-releasing intrauterine system used in combination with transdermal estradiol is a good option for women requiring contraception.

Principles for HRT prescription for women affected by POI are similar to those for women experiencing menopause at the usual age. A list of HRT (MHT) preparations available in Australia can be found on the Australasian Menopause Society website (www.menopause.org.au/hp/information-sheets/426-ams-guide-to-equivalent-mht-hrt-doses). The usual contraindications apply, and include current or suspected oestrogen-dependent cancers and active liver, cardiovascular or venous thromboembolic disease. Although the evidence is limited, HRT does not appear to increase breast cancer risk in women with POI, and the risk appears to be less with oestrogen

2. PREMATURE OVARIAN INSUFFICIENCY: RESOURCES FOR PATIENTS

Ask Early menopause App
www.askearlymenopause.org

Australasian Menopause Society
www.menopause.org.au

Healthtalk Australia early menopause resource
https://healthtalkaustralia.org/early-menopause-experiences-and-perspectives-of-women-and-health-professionals

Jean Hailes for Women's Health
www.jeanhailes.org.au

Daisy Network
www.daisynetwork.org/locations/countries/daisy-in-australia

alone than with combined oestrogen and progestin in studies of postmenopausal women of typical age. *BRCA* gene mutation carriers can use short-term HRT following prophylactic bilateral salpingo-oophorectomy without an apparent increase in breast cancer risk.[29] After the age of 51 years (average age of natural menopause), consideration of whether to use HRT/MHT is the same as for any postmenopausal woman.

There are limited data for the use of testosterone therapy in POI. One small trial in women with Turner syndrome showed that testosterone therapy improved lipid profile, BMD, body composition, cognitive function, quality of life and sexual desire.[30] However, studies of women with normal karyotype idiopathic POI indicated that testosterone was no different to placebo for BMD or quality of life.[17,31]

Karima was advised to use HRT rather than the COC for management of her POI due to her desire for fertility. A cyclical HRT regimen was chosen because the development of amenorrhoea may indicate pregnancy.

What other options can be offered if Karima prefers not to have HRT?

HRT is the best treatment in POI and should be strongly recommended unless there are contraindications. If HRT is contraindicated, nonhormonal options may be considered for vasomotor symptoms. Serotonin noradrenaline reuptake inhibitors, selective serotonin reuptake inhibitors, clonidine, and gabapentin have all been shown to reduce vasomotor symptoms in women with a history of breast cancer (off-label use except for clonidine).[32] Cognitive behavioural therapy has been shown to reduce vasomotor symptoms and improve mood, sleep, sexual function and quality of life. Nonhormonal vaginal moisturisers or lubricants can be used for urogenital symptoms.[1] Cardiovascular health should be monitored carefully, and referral to an endocrinologist for management of bone health should be considered.

What fertility advice should be given to Karima?

Spontaneous resumption of ovarian activity has been reported in 25% of women with idiopathic POI,[33] usually within the first year after diagnosis, with a spontaneous pregnancy rate of 5%.[34] Therefore, contraception needs to be considered in the choice of HRT if a woman does not want to become pregnant. However, in the case of desired fertility, women with POI should be referred to a fertility specialist for assessment. Currently, oocyte donation is the best method to achieve a pregnancy.

Karima and her husband were referred to a fertility specialist.

Conclusion

POI can have profound effects on a woman's physical and psychosocial wellbeing that require multimodal assessment and management. Prompt diagnosis, institution of individualised HRT, psychological support, provision of information and monitoring for long-term sequelae are essential components of management. Referral to psychological, genetic, endocrinology and fertility services may also be required. MT

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A list of references is included in the online version of this article (www.medicinetoday.com.au).

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Premature ovarian insufficiency
Not 'too young for menopause'

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Vulvovaginal symptoms after menopause

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Vulvovaginal atrophy causes significant morbidity in women as they age. The primary care physician is in a unique position to use a consultation to discuss a woman's symptoms with her and to explain the treatment options.

Urogenital health is an essential part of the postmenopausal years in women, from midlife until the end of life. Loss of oestrogen after menopause together with the effects of ageing leads to physical changes and symptoms that may have an impact on a woman's health, wellbeing, intimacy and quality of life.

Many women who experience symptoms after menopause, such as vaginal dryness, pain with intercourse, incontinence and vulvovaginal irritation, never mention these symptoms when they visit their doctor because they are embarrassed, shy, or feel that is what happens after menopause, so they accept it. The changes may worsen with time, potentially leading to major interference with a woman's daily life and major psychosocial consequences, including depression and social anxiety.

The GP is the person whom a woman is most likely to trust sufficiently to discuss her genitourinary symptoms with. Appropriately and respectfully initiating questions about these symptoms and signs may allow the woman to discuss her experience and receive the help she needs. The vulva and vagina should always be examined when there are symptoms.

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Urogenital changes after menopause

Oestrogen receptors, both alpha and beta, are found in the vagina, urethra, the trigone of the bladder, levator ani muscles, pelvic fascia and supporting ligaments. After menopause, the expression of these receptors diminishes.[1] After the cessation of periods, oestrogen levels fall, affecting the urogenital tissues (Box 1).

The loss of oestrogen leads to changes in function in the vagina, urethra and bladder, and in sexual functioning, resulting in one or many symptoms. These may include:

- vaginal dryness and loss of lubrication with sex
- pain or discomfort with sexual intercourse and bleeding after sexual intercourse
- urinary frequency, urinary urgency or dysuria
- increased urinary tract infections
- dryness, irritation, burning or itching of the vulva
- an increase in genital infections or discharge[2]
- changes in sexual desire, arousal and orgasm.

These may also be combined with other menopause symptoms, such as:

- vasomotor symptoms
- aches and pains
- poor sleep
- mood changes.

Quality of life may be impaired as these symptoms can affect body image, relationships, work and social activity.

Risk factors for development of genitourinary symptoms include: menopause, premenopausal bilateral salpingo-oophorectomy, premature ovarian failure, other hypoestrogenic states such as hypothalamic amenorrhoea and the postpartum period, cancer treatments including chemotherapy, pelvic irradiation and adjuvant therapies, decreased frequency or absence of sexual activity, lack of vaginal birth and lifestyle factors of smoking and alcohol abuse.

1. EFFECTS OF LOWERED OESTROGEN LEVELS ON FEMALE UROGENITAL TISSUES

- Thinning of the vaginal walls
- Loss of rugae, leading to smooth vaginal walls
- Changed vaginal microbiome due to loss of an acidic environment
- Altered immune response in the vagina
- Reduced blood flow to the vagina and pelvis
- Fragile mucosal surfaces including inflammation, petechiae, pallor and fissuring
- Narrowing of the vaginal fornices
- Shortening and narrowing of the vagina
- Loss of collagen and tissue elasticity, which may lead to introital stenosis or an increase in prolapse symptoms
- Introital narrowing and stenosis with eversion of the urethral meatus
- Loss of vulval fatty tissue
- Atrophy of the labia minora and majora, including the clitoral hood
- Slightly decreased urethral closure pressure; also occurs as women age, leading to incontinence
- Thinning of the urethral and bladder trigone epithelium
- Weakening of the pelvic floor tissues and supporting structures

Epidemiology of genitourinary symptoms

About 50% of peri- and postmenopausal women report genitourinary symptoms, primarily vaginal dryness and pain with intercourse but, less frequently, vulvovaginal irritation, itching and soreness. About 25% of women seek help but some report their health professional is dismissive of their complaints as normal ageing.[3]

In the Vaginal Health: Insights, Views and Attitudes survey, 55% of participants reported symptoms but only 4% attributed them to vaginal atrophy. In the same survey sexual dysfunction symptoms caused the greatest adverse impact on life, because of dryness, pain with intercourse, loss of desire, less intimacy and reduced sexual frequency.[4]

Women may have signs of atrophy but no symptoms. In the Women's Health Initiative Hormone Study, about 70% of women at the enrolment examination had clinical evidence of vulvovaginal changes, but only 10% reported moderate to severe genital dryness.[5]

Among women who have symptoms, some do not realise their cause and that they can seek help; others may be too embarrassed to discuss these symptoms; whereas others do not feel listened to when they seek help. Some women may mention these symptoms because their partner has been complaining and insisting they speak to the doctor about them.

As women age, general health and wellbeing can diminish with illness. This decline can be compounded by bladder, vulval and vaginal symptoms if they are untreated. Menopause symptoms such as vasomotor symptoms mostly improve with time, but the genitourinary symptoms do not. Once a woman has genitourinary symptoms, they tend to worsen with time, so it is important to let the woman know this and offer appropriate treatment.

Some vulval changes occur due to menopause; however, other vulval conditions also increase in prevalence after menopause. These conditions include lichen sclerosus, lichen planus and lichen simplex chronicus, all of which present with similar symptoms and need to be diagnosed and managed long-term.

How to improve management and treatment

History and examination

A woman may present for a general check or for a cervical screen. This consultation can be used to ask about genitourinary and bowel symptoms.

When a postmenopausal woman presents with genitourinary symptoms, it is important to make her feel at ease, as she may be very anxious about talking about her symptoms. Ask her to describe her symptoms, how long she has experienced them and how they impact on her life.

You may need to ask further questions. Try not to use technical terms, but rather, language she understands. This will depend on her level of health literacy.

The term 'vaginal atrophy' is not liked; preferably use the words 'vaginal dryness' or 'vaginal discomfort', which help to lead into questions about sex and pain, dryness and lack of libido. Sometimes starting a discussion about urinary symptoms is a way to then ask specific questions about her symptoms relating to dryness and pain.

A health professional should examine their own attitudes in having a consultation about genitourinary symptoms including dyspareunia and other aspects of sexual function. Reasons for difficulty in a consultation may be:

- a lack of time
- a lack of experience and training
- embarrassment for either themselves or the woman
- personal or religious beliefs about sexuality and genitalia.[6]

The history should also include the woman's menstrual, gynaecological, obstetric and sexual history as well as any other relevant surgical, medical, psychosocial and family history. If possible, a long appointment should be planned to allow time.

Examination of the vulva and vagina

An examination should always be performed respectfully to make the woman as comfortable as possible. Having a chaperone may be appropriate.

After performing the general examination, first examine the vulva, looking for signs of the atrophic changes of the vulval tissues, the labia, the urethral meatus and the introitus. Look at the colour, signs of pallor or redness, any masses, narrowing or stenosis and thickening of the tissue. Always remember to also look around the anus, as changes may occur there in such conditions as lichen sclerosus. Where there is inflammation or redness, take a swab for microscopy and culture to exclude any bacterial infection.

Perform a vaginal examination, observing the signs outlined above, and exclude any pelvic abnormality. Samples for

microscopy and culture should be collected if there is a vaginal discharge (vaginal swab) or any urinary symptoms (mid-stream urine).

Management

Vulval dryness

Some women experience vulval dryness and will benefit from using an over-the-counter product for external use, such as petroleum jelly, which forms a barrier, or an intensive treatment ointment that similarly protects and also soothes the skin. The vulval skin requires gentle care, and it is important to instruct the woman in vulval care (Box 2).

Providing written information is helpful. Australasian Menopause Society information leaflets are available online (https://www.menopause.org.au/health-info), and detailed consumer information is also available from Jean Hailes for Women's Health (https://www.jeanhailes.org.au/health-a-z).

Vaginal dryness and discomfort with intercourse

Initially, simple measures to help vaginal dryness and discomfort may be recommended. Using a vaginal moisturiser reduces dryness by effectively rehydrating the vaginal mucosa. The products available are used about every third day.

Lubricants, used at the time of intercourse, will help to make intercourse more comfortable. Using oils such as olive oil or sweet almond oil can be effective. Commercially available lubricants are not all the same as each other and some may cause side effects; therefore, recommend products that are similar to vaginal secretions in their pH and osmolality.[7]

Vaginal oestrogens

Vaginal oestrogens have been shown to be very effective in the treatment of vaginal dryness, dyspareunia, urinary urgency and recurrent urinary tract infection.

Products available in Australia are low-dose estradiol vaginal tablets and low-dose estriol vaginal cream or pessaries. Initial treatment is recommended daily for two weeks, then twice per week as a maintenance dose. When the vaginal tissue is atrophic, there is some initial absorption into the systemic circulation, but this diminishes once the vaginal tissues become oestrogenised and are thicker. A progestogen is not needed, even in a woman with a uterus, if only vaginal oestrogen is used.

The blood supply to the vagina is twofold; the upper vaginal venous flow is to the utero-vaginal plexus and the lower vagina, especially the anterior vaginal wall to the haemorrhoidal and pudendal venous plexus. This insight allows us to target vaginal oestrogen to the appropriate areas, with application to the lower vagina when there are introital and lower vaginal atrophy and bladder symptoms.[8]

Systemic menopausal hormone therapy may treat the vulvovaginal symptoms, but in a small percentage of women who use systemic therapy, atrophic symptoms and signs persist and a local vaginal oestrogen is required in addition.

Vaginal laser therapy has been used in patients in whom oestrogen products were contraindicated, but the potential risks and lack of long-term data on this treatment are concerning. It is not TGA-approved for treating menopausal symptoms.

Two products that are not available in Australia would increase the treatment options. These are ospemifene, an oral selective estrogen receptor modulator (SERM), and intravaginal prasterone (dehydroepiandrosterone [DHEA]). Ospemifene is oestrogenic on the vagina and has been shown to improve vaginal dryness and dyspareunia. It has a slight oestrogenic effect on the endometrium (endometrial hyperplasia rate, 0.3%) and small potential effect of deep venous thrombosis, similar to other SERMs. Side effects include hot flushes. There are no long-term breast cancer safety studies for ospemifene. Intravaginal prasterone is a vaginal insert (pessary) of 0.5% DHEA that effectively reduces symptoms of vaginal dryness and dyspareunia. The main side effect is vaginal discharge. There are no long term safety studies in breast cancer for prasterone.[10,11]

2. PRACTICAL TIPS FOR WOMEN REGARDING VULVAL CARE

- Do not use soap; use plain water or a soap substitute
- Do not scrub or use antiseptics or vaginal douching
- Wear 100% cotton underwear, preferably washed in pure soap
- Do not sit in wet swimwear; change out of swimwear and shower to remove chlorine or salt from the vulva immediately after swimming
- Change out of lycra gym wear after exercise
- Avoid tight pants/jeans, g-strings and pantyhose
- Use white, unscented toilet paper
- Always wipe the vulva and anus from front to back
- Use 100% cotton pads or panty liners

Conclusion

Vulvovaginal atrophy causes significant morbidity in women as they age. Acceptance, embarrassment or lack of knowledge can cause a woman to not seek help for her symptoms. The primary care physician is in a unique position to use a consultation to discuss her symptoms.

History-taking and examination will allow exclusion of skin conditions such as lichen sclerosus, which has the long-term risk of vulval cancer. Appropriate management is dependent on risk factors. There are many treatments available, including lubricants and moisturisers, vaginal oestrogen products and systemic menopausal hormone therapy. MT

References

A list of references is included in the online version of this article (www.medicinetoday.com.au).

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Vulvovaginal symptoms after menopause

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Postmenopausal osteoporosis

Is there a role for menopausal hormone therapy?

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Menopausal hormone therapy (MHT) increases bone density and prevents fracture. However, the publication and accompanying media coverage of the Women's Health Initiative study made many women fearful of MHT and many doctors reluctant to prescribe it. There is increasing recognition that MHT does have a place in health management of postmenopausal women, including for fracture prevention.

To paraphrase Professor Bronwyn Stuckey, menopause is a consequence of improved public health: most women now not only survive childbirth but also their childbearing years and live long enough to experience loss of ovarian function (at an average age of 51 years). Menopause is generally rare among mammals, occurring only in humans, short-finned pilot whales and killer whales.[1]

This article focuses on the use of menopausal hormone therapy (MHT) with respect to bone health, and discusses the evidence for combined oestrogen–progestogen therapy, oestrogen-alone therapy in women who have had a hysterectomy, selective oestrogen receptor modulators (SERMs), tissue-selective oestrogen complexes (TSECs) and tibolone. Use of MHT in glucocorticoid-induced osteoporosis, premature or early menopause (cessation of menses before the age of 40 or 45 years, respectively) and functional hypothalamic amenorrhoea (e.g. anorexia nervosa) is not covered.

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MHT and bone

Oestrogen

It is hard to overestimate the importance of oestrogen to the skeleton. The rapid rise in bone mineral density (BMD) from increasing levels of gonadal hormones at puberty is predominantly due to oestrogen, in both sexes. Oestrogen secretion causes growth plate closure and thus determines a person's final height. Oestrogen is important for osteoblasts, osteoclasts and osteocytes and maintains both cortical and trabecular bone.[2] It also mediates the skeleton's response to mechanical loading via sclerostin suppression.[3]

Oestrogen deficiency causes rapid bone loss at menopause – with greater than 10% of bone mass at the lumbar spine and greater than 9% at the femoral neck being lost in the decade after menopause, mostly in the year before and two years after the final menstrual period – and contributes to ongoing bone loss thereafter.[4]

The four major endogenous oestrogens

KEY POINTS

- Oestrogen-alone and combined oestrogen–progestogen therapies increase bone mineral density and reduce vertebral and nonvertebral fractures in postmenopausal women.
- Use of menopausal hormone therapy (MHT) in general, and for osteoporosis specifically, has been controversial since the early closure of the Women's Health Initiative (WHI) study.
- In the final analysis of the WHI study, the benefits of MHT were found to be considerable and, particularly for younger, recently postmenopausal women, may outweigh the risk of harm.
- Commencing MHT is a valid option for postmenopausal women under the age of 60 years and within 10 years of menopause, with no specific contraindications, not only for vasomotor symptoms but also for bone protection.

are oestrone, oestradiol, oestriol and oestetrol, with oestradiol being the most biologically active form. There are multiple pharmacological oestrogen formulations available in Australia, including 17-beta oestradiol, combined oestrogens and the synthetic oestrogens ethinylestradiol and mestranol. Conjugated equine oestrogens (CEEs), originally derived from pregnant mares' urine, contain various oestrogens, with the predominant form being oestrone sulfate, which is metabolised to oestrone and then oestradiol.

Oestrogen binds to nuclear oestrogen receptors (ERs). There are two subtypes (ER-alpha and ER-beta), expressed differently in different tissues, with ER-alpha the predominant ER in cortical bone, breast and endometrium. Upon ligand binding, ERs undergo conformational change and dimerisation, ultimately affecting DNA transcription.[2]

In the 1970s, the use of oestrogen-alone therapy in women with an intact uterus caused endometrial hyperplasia and increased the risk of endometrial cancer. These complications were almost entirely obviated by the addition of progesterone, particularly if given continuously.[5]

Use of intravaginal oestrogen has a theoretical risk of endometrial hyperplasia; however, compared with placebo or baseline incidence rates, no increase in endometrial hyperplasia or carcinoma has been observed at 12 months, using endometrial biopsy or ultrasound, respectively.[6,7] Data regarding long-term risks are lacking, but progesterone coadministration is generally thought unnecessary.[8]

Selective oestrogen receptor modulators and tissue-selective oestrogen complexes

SERMs have oestrogenic effects in some tissues (e.g. bone) but oestrogen-antagonistic effects in others (e.g. breast and uterus). Similar to oestrogen, SERMs interact with nuclear ERs. The tissue-specific agonist versus antagonist effects of SERMs depend not only on ER subtype distribution and binding, but also on differing compositions of the ER–ligand complex, its dimerisation and conformational change, and the coactivators and/or corepressors available in any particular cell type.[9]

Two SERMS are available in Australia: raloxifene and bazedoxifene. Lasofoxifene, another SERM, is currently unavailable. At the endometrium, raloxifene has a neutral effect (as does lasofoxifene), whereas bazedoxifene is antioestrogenic.[10] Thus, bazedoxifene can be coadministered with oestrogen without additional endometrial protection.[11]

TSEC therapy refers to the combination of a SERM plus oestrogen and is available in Australia as bazedoxifene plus CEE.

Tibolone

Tibolone is a biologically inactive synthetic steroid, but its three active metabolites are weak agonists of the ER (e.g. bone and vaginal tissue), progesterone receptor (e.g. endometrium) and androgen receptor.

Progestogens

Progesterone is the major progestogen in humans and is secreted predominantly by the ovaries, affecting the uterus, vagina, cervix, breasts and brain. Progesterone binds to the progesterone receptor (both nuclear and membrane forms) and to other nonaromatised steroid receptors; namely, androgen, glucocorticoid and mineralocorticoid receptors. For example, progesterone antagonises aldosterone at the mineralocorticoid receptor, altering fluid balance during the menstrual cycle.

There are many progestogens available in Australia. Progesterone itself is available orally as micronised progesterone. Synthetic progestogens (collectively termed progestins) include medroxyprogesterone acetate, etonogestrel, levonorgestrel, dydrogesterone, drospirenone and norethisterone. Progestogens are also available in combination with oestrogen, in both oral and transdermal formulations. In addition to binding to the progesterone receptor,

TABLE 1. FRACTURE OUTCOMES OF MENOPAUSAL HORMONE THERAPY FROM THE WOMEN'S HEALTH INITIATIVE STUDY[18,19]

Outcome	Hazard ratio (95% CI)*	
	Oestrogen alone	Oestrogen–progestogen
Hip fractures	0.61 (0.41–0.91)	0.66 (0.45–0.98)
Vertebral fractures	0.62 (0.42–0.93)	0.66 (0.44–0.98)
Total fractures	0.70 (0.63–0.79)	0.76 (0.69–0.85)

* Nominal rather than adjusted figures from Women's Health Initiative publications are presented.

different progestogens have varying profiles at the other steroid receptors. Thus, side effects differ between agents.

Androgens

Androgens affect the skeleton indirectly (via aromatisation to oestradiol and the ER) and possibly directly (through the androgen receptor).[12] In hypogonadal men, the main mechanism by which testosterone prevents bone loss is through conversion of testosterone to oestradiol.[13] A meta-analysis on the safety and efficacy of testosterone in women did not show any effect of testosterone on BMD.[14] In women, an independent effect of testosterone on bone remains poorly defined.[15]

Dehydroepiandrosterone (DHEA) and DHEA-sulfate

Dehydroepiandrosterone (DHEA) is derived predominantly from the adrenal cortex (90%), with only 10% produced by the gonads. DHEA-sulfate (DHEA-S) is produced almost exclusively by the adrenal gland. Both DHEA and DHEA-S can be metabolised to oestrogens and androgens. Their contribution to overall postmenopausal gonadal hormone levels (which are, in any case, low) is not well defined. Whether either has an independent skeletal effect is unknown.

Does MHT improve bone health?

Oestrogen-alone and combined oestrogen–progestogen therapies

Both oestrogen-alone and combined oestrogen–progestogen therapies improve BMD and prevent vertebral and nonvertebral fractures (including hip fractures) in postmenopausal women.

Two randomised controlled trials (RCTs) showed oestrogen improved BMD,[16,17] consistent with observational data that it decreased fracture risk. The Postmenopausal Estrogen/Progestin Interventions Trial (PEPI) demonstrated efficacy of MHT in improving BMD. The trial enrolled 875 healthy women aged 45 to 64 years (mean age 56) within 10 years of menopause, who were randomly assigned to receive either placebo or one of four active regimens, CEE 0.625 mg/day alone, or combined with medroxyprogesterone acetate (either cyclically or continuously), or micronised progesterone. Participants assigned to the placebo group lost 1.8% BMD at the lumbar spine and 1.7% at the hip at 36 months, whereas those in the active regimen groups gained BMD at the hip and spine. CEE with continuous medroxyprogesterone acetate use was associated with a significantly greater increase in spinal BMD (5%) compared with the other three active regimens (3.8%).[16]

One of the indisputable findings of the Women's Health Initiative (WHI) study, involving 27,347 women, was that MHT reduced fracture risk. The trial included participants aged 50 to 79 years who were not stratified by baseline BMD and received either CEE 0.625mg/day plus medroxyprogesterone acetate 2.5 mg/day (n=8506) or placebo (n=8102). Compared with placebo, oestrogen alone reduced hip, clinical vertebral and total fractures by 30 to 39%, and oestrogen–progestogen therapy reduced fractures by 24 to 34% (Table 1).[18,19]

Later analyses of the WHI data found that the positive effect of MHT on bone health persisted after treatment discontinuation for up to five years, although unsurprisingly, the degree of protection decreased over time.[20] However, the placebo-controlled Women's International Study of Long-Duration Oestrogen after Menopause (WISDOM) RCT, evaluating the long-term risks and benefits of MHT in postmenopausal women aged 50 to 69 years, prematurely closed during recruitment after early findings from the WHI study suggested an increased cardiovascular risk associated with stopping MHT. With less than a year's follow up and only 26% of required recruitment (22,300 planned to ensure adequate power), little can be concluded from this study.[21]

A 2016 systematic review and meta-analysis of 28 studies involving 33,426 women found fracture risk reduced with MHT use, with a relative risk (RR) of 0.74 for total fractures (95% confidence interval [CI], 0.69–0.80), 0.72 for hip fractures (95% CI, 0.53–0.98) and 0.63 for vertebral fractures (95% CI, 0.44–0.91).[22]

Does the dose and/or formulation of MHT matter?

Different doses and preparations of MHT may have differing effect sizes on bone health. Data regarding the efficacy of low-dose oestrogens and transdermal oestrogens are scarce. A small 2019 Chinese study of 123 women in early menopause comparing half dose of CEE (0.3 mg) with the standard dose (0.625 mg) combined with progesterone found that, although half dose CEE increased overall BMD and decreased bone turnover markers, standard MHT dose was more efficacious in increasing BMD at the lumbar spine.[22] The Million Women Study showed that oral oestrogen was associated with a greater decreased fracture risk than transdermal oestrogen (hazard ration [HR], 0.60; 95% CI, 0.53–0.68 *vs* HR, 0.76; 95% CI, 0.65–0.86; p=0.04).[23] The meta-analysis suggested that oestradiol use was associated with a greater decrease in total fracture risk than CEE (p=0.01).[22] Although small trials have shown that intravaginal oestrogen

improves BMD, fracture data are lacking.[24,25] Intravaginal oestrogen is not recommended for bone health.

MHT may have synergistic effects with calcium and vitamin D on bone health. In the calcium plus vitamin D arm of the WHI study (16,089 participants), women receiving MHT (either oestrogen alone or oestrogen–progestogen) and calcium plus vitamin D had a lower risk of hip fracture compared with women taking calcium plus vitamin D but not MHT (HR, 0.58; 95% CI, 0.37–0.93 *vs* HR, 1.15; 95% CI, 0.81–1.61; p for interaction, 0.07).[26-28] However, within the group of women taking MHT, there is no direct available comparison between those who did and did not receive calcium plus vitamin D.[16]

Do oestrogen-alone and oestrogen–progestogen therapies benefit all postmenopausal women or only those at highest risk of fracture?

The WHI study population was unusually healthy from a bone perspective; hip fracture rates in the placebo group were about 50% lower than expected for an age-matched cohort.[21] Nonetheless, a reduction in all fracture types was observed in both study arms. BMD was only measured in 5.7% of participants, and this subgroup was not thought to be representative of the cohort overall. Thus, the capacity of the WHI to assess who best to target for fracture prevention (women with low BMD and osteoporosis or osteopenia, women with other clinical risk factors for fracture, or all postmenopausal women) is limited.

In the oestrogen-alone arm, 'the effect of CEE on hip and total fractures was remarkably consistent, almost irrespective of individual characteristics'.[29] A summary fracture risk score (including age, current smoking status, body mass index and previous fracture, but not BMD) was calculated. There was significant interaction between this score and total fracture risk reduction, such that those with the highest fracture risk score had the greatest reduction in total fracture risk (high risk: HR, 0.66; moderate risk: HR, 0.68; lowest risk: HR, 0.86; p for interaction, 0.04). A similar but nonsignificant trend was observed for risk of hip fracture specifically. Total hip BMD was measured at baseline in 938 women: 5.7% had a T-score less than –2.5 and 38.7% had a T-score between –1 and –2.5. Within this small group, total fracture risk reduction with CEE was insignificant (49 fractures with CEE *vs* 64 with placebo; HR, 0.77), and no significant interaction of fracture risk reduction with BMD was observed (osteoporotic group: HR, 0.83; osteopenic group: HR, 0.83; women with normal BMD: HR, 0.99; p for interaction, 0.17).

In the combined oestrogen–progesterone arm, similar but not identical analyses were performed. Reduction in risk of hip fracture was observed regardless of baseline characteristics, with the single exception that reduction in hip fracture risk was only observed in women with a daily calcium intake greater than 1200 mg.[30] No interaction was seen between the summary fracture risk score and either hip fracture or total fracture risk reduction. Total hip BMD was measured in 1024 women, and women with a T-score less than –3.0 were excluded from participation. The risk reduction for all fractures in women with a T-score less than –2.5 was 0.53 (with a CI crossing 1; no formal p value was presented), compared with 0.87 in the group with BMD greater than –2.5 (p for interaction of fracture reduction with BMD, 0.15). It is unclear how many women overall had a T-score less than –2.5, and the fracture numbers were small (e.g. 11 fractures with combined oestrogen–progesterone *vs* 22 with placebo in the low BMD group).[30]

In 2022, a post hoc combined analysis of 25,389 postmenopausal women aged 50 to 79 years enrolled in the two WHI trials was performed to determine if the antifracture efficacy of MHT differed by baseline falls and fracture risk. Compared with placebo, MHT was associated with a significantly reduced risk of any clinical fracture (HR, 0.72; 95% CI, 0.65–0.78), major osteoporotic fracture (clinical spine, hip, forearm or humerus) (HR, 0.60; 95% CI, 0.53–0.69) and hip fracture (HR, 0.66; 95% CI, 0.45–0.96), regardless of baseline fracture risk and falls risk.[31] In extracting meaning from these results, even if the relative risk reduction is the same across the population, the absolute reduction in fractures will be greatest in the group with the highest fracture rate.

SERMs and TSECs

SERMs improve BMD and prevent vertebral fracture. Among 6828 women in the Multiple Outcomes of Raloxifene Evaluation (MORE) trial, raloxifene improved BMD at the femoral neck and spine and reduced vertebral fractures (RR, 0.7; 95% CI, 0.5–0.8, p=0.05).[32] However, it had no effect on nonvertebral fractures (RR, 0.9; 95% CI, 0.8–1.1; p=0.24) or hip fractures (RR, 1.1; 95% CI, 0.6–1.9; p=0.71).[32] Bazedoxifene has similar efficacy to raloxifene in terms of increased BMD at the hip and spine and vertebral fracture prevention.[33] In contrast, lasofoxifene reduces both vertebral and nonvertebral fractures.[34] In a 2019 network meta-analysis, both raloxifene (RR, 0.59; 95% CI, 0.46–0.76) and bazedoxifene reduced vertebral fracture (RR, 0.61; 95% CI, 0.41–0.90).[35]

TSECs may be more effective for osteoporosis prevention than SERMs alone. The Selective Estrogen Menopause and Response to Therapy (SMART-1) trial found greater BMD gains at the lumbar spine and hip with a TSEC (bazedoxifene plus CEE) compared with either raloxifene alone or placebo, although this study was not adequately powered for fracture comparison.[36]

Tibolone

Tibolone prevents bone loss, increases BMD and prevents fracture.[27,37,38] The Long-Term Intervention on Fractures with tibolone (LIFT) study, involving 4538 women, showed that tibolone significantly reduced vertebral fractures at the low dose of 1.25 mg daily (standard dose 2.5 mg daily)(HR, 0.55; 95% CI, 0.41–0.74; p <0.001) and nonvertebral fractures (HR, 0.74; 95% CI, 0.58–0.93; p=0.01) compared with placebo.[37] A recent meta-analysis of 107 studies that included tibolone confirmed that tibolone reduced both vertebral (RR, 0.56; 95% CI, 0.36–0.87)

and nonvertebral fractures (RR, 0.73; 95% CI, 0.58–0.94) compared with placebo.[35]

Isolated progestogen

Whether progesterone has a direct skeletal effect is unresolved.[39] The isolated use of progestogens (including transdermal preparations from compounding pharmacies) to prevent or treat osteoporosis is of unproven benefit. Supraphysiological doses, as are used in progestin-only contraceptives, are associated with bone loss (through hypogonadotrophic hypogonadism and secondary oestrogen deficiency), although this appears to be reversible, and increased fracture risk has not been reported.[40,41] High-dose progestogens may also stimulate glucocorticoid receptors.[39] At lower doses, progestogens may act synergistically with oestrogen: combined oestrogen–progestogen increases BMD about 1% more than oestrogen alone.[42] This difference is statistically significant, but whether it is clinically meaningful is debatable.

Androgens

Although some multivariate analyses suggest an independent effect of testosterone on BMD and fracture risk in women, parsing unique and independent effects of individual sex steroids is difficult, even in an experimental setting.[12] Moreover, testosterone does not consistently improve BMD, even allowing for its aromatisation to oestradiol.[43,44] Data regarding fracture outcomes and cardiovascular safety are lacking. Testosterone is not recommended for treating postmenopausal osteoporosis.

DHEA and DHEA-S

In ovariectomised mice, DHEA-S showed some oestrogen-independent effects preventing bone loss.[45] The clinical relevance of this finding for humans is unclear. A recent multivariate analysis suggested that DHEA-S levels correlated with BMD in both men and women, but this study did not adjust for other sex hormones, including oestrogen.[46] Robust evidence that DHEA or DHEA-S independently improves BMD or reduces fracture risk is lacking.[43]

How does MHT compare with other options for treating osteoporosis?

Pharmacological management of postmenopausal osteoporosis was presented in a US Endocrine Society clinical practice guideline.[47] A meta-analysis of pharmacological therapies for postmenopausal women (107 trials involving 193,987 postmenopausal women) found that MHT (oestrogen alone *vs* oestrogen–progestogen), bazedoxifene, raloxifene, lasofoxifene, tibolone, bisphosphonates, teriparatide and denosumab are all effective treatments for osteoporosis.

All forms of MHT are effective in preventing vertebral fractures. Oestrogen alone and oestrogen–progestogen are effective for preventing hip fractures, whereas neither SERMs nor tibolone are effective for this outcome.[35] Most pivotal trials of bisphosphonates, denosumab and SERMs are in older postmenopausal women; trials in younger postmenopausal women have usually assessed BMD rather than fracture as the primary outcome.[48,49]

There are few head-to-head studies comparing MHT with other treatments for osteoporosis, whether assessing BMD or fracture, and entry criteria differ considerably between trials. A study in young postmenopausal women aged 45 to 59 years found similar increases in BMD with alendronate versus combined oestrogen–medroxyprogesterone acetate.[49] In contrast, a study of older postmenopausal women (aged 65 to 90 years) found greater increases in BMD with alendronate compared with oestrogen (with or without medroxyprogesterone).[50] Neither study assessed fracture risk. In considering MHT versus bisphosphonates, bone loss will restart promptly after cessation of MHT, whereas the effect of bisphosphonates may persist after cessation (the duration of persistence varies with different compounds).[51]

Combination treatment

Trials combining MHT with bisphosphonate therapy have produced contradictory results.[50,52,53] A small study of 331 postmenopausal women with osteoporosis compared raloxifene, alendronate and both therapies combined. Combination therapy resulted in greater BMD gains than either medication alone.[54] There is no clear role for these combinations at present.

Limited studies combining MHT (including raloxifene) with teriparatide show greater BMD gains.[55] No trials have combined MHT with denosumab.

Given its efficacy, why is MHT so controversial?

Two decades ago, oestrogen-alone and combined oestrogen–progestogen therapies were widely used by postmenopausal women. In addition to reducing vasomotor symptoms, observational studies (e.g. Nurses' Health Study) suggested that MHT was beneficial for cardiovascular health.[56] Other studies (e.g. Framingham Study) did not support these findings.[57] The WHI study was established specifically to assess the effect of MHT on cardiovascular health, with recruitment deliberately skewed towards older women (almost 70% of participants were aged 60 years or older).

The WHI compared placebo with oestrogen-alone (CEE) in 10,739 women who had undergone hysterectomies and compared placebo with combined oestrogen–progestogen treatment (CEE and medroxyprogesterone acetate) in 16,608 women who had not had hysterectomies.[58] Secondary outcomes included breast cancer, colon cancer, stroke, thromboembolism and fracture risk. Both WHI arms were terminated early – the combined therapy arm in 2002, after 5.2 years, and the oestrogen-alone arm in 2004, after 6.6 years. The termination of the oestrogen–progestogen arm was announced in a publication alongside a contemporaneous press release – without prior knowledge of the principal investigators, and before final analyses had been done.[59] Subsequent (and final) analyses of the WHI study have not necessarily agreed with the initial publications, particularly their tone.

Around the same time, results of the Million Women Study, an observational study of 1,084,110 women with longitudinal follow up, were also published. This study concluded that invasive breast cancer

was increased in women currently using MHT, particularly those using combined MHT, compared with those who had never used it.[60]

Consequently, MHT prescribing declined drastically worldwide, including in Australia.[61] Some studies have since suggested a decrease in breast cancer incidence in women over the age of 50 years, attributed to the decreased use of MHT. For example, a 6.7% decrease in the incidence of breast cancer in Australia was reported in the year after publication of the WHI trial, although this would be inconsistent with the usual timeframe between cancer initiation and clinical presentation.[62] Other changes during this time included increased intensity of breast cancer screening regimens in multiple countries (including the United Kingdom and Australia), increased rates of obesity and reduced rates of smoking. Notably, in 2007, there was a 34% increase in breast cancer compared with expected rates projected from 1987, despite widespread abandonment of MHT.[63]

More recently, there has been increasing recognition that the risks and benefits of MHT are more nuanced than were initially presented and that, for many women, MHT may be both beneficial and low risk.[59]

WHI and cancer risk

Breast cancer

Initial publications and press releases from the WHI study strongly implied that MHT increased the risk of breast cancer. However, the data showed that oestrogen alone did not increase breast cancer, with an absolute risk of seven fewer cases of invasive breast cancer per 10,000 person-years of treatment in the oestrogen-alone arm compared with placebo.[18] Combined oestrogen–progestogen slightly increased the risk of invasive breast cancer and all breast cancer, with an absolute risk of nine breast cancer cases per 10,000 person-years of treatment (i.e. less than 0.1% per person-year; Table 2).[16,17,19,56] This risk is similar to that seen with postmenopausal obesity and decreased physical activity.[64,65] Importantly, extended follow up (18 years, including the intervention phase) found no difference in mortality from breast cancer in the pooled intervention arms compared with placebo.[66]

Two recent nested case-control studies analysed data from 98,611 women with breast cancer aged 50 to 79 years and 457,498 matched controls, to investigate the association between MHT and breast cancer risk. In these studies, short-term MHT use was defined as use for less than five years; long-term use was defined as use for more than five years. Recent MHT use was defined as a prescription more than one year and less than five years before the index date, whereas past exposure was defined as those who had used MHT more than five years prior to the index date. These studies found that both short-term and long-term use of oestrogen-only and combined oestrogen–progestogen therapies were associated with an increased risk of breast cancer compared with never having used MHT. The odds ratio for oestrogen-only therapy was 1.15 (95% CI, 1.09–1.21) and for combined oestrogen–progestogen therapy was 1.79 (95% CI, 1.73–1.85). The highest risk for combined progestogens was for norethisterone (RR, 1.88; 95% CI 1.79–1.99) and the lowest risk was for dydrogesterone (RR, 1.24; 95% CI, 1.03–1.48). These studies found that both short-term (including current) use of oestrogen-only therapy (OR, 1.15; 95% CI, 1.09–1.21) and combined oestrogen–progestogen therapy (OR, 1.79; 95% CI, 1.73–1.85) were associated with an increased risk of breast cancer compared with never having used MHT. Additionally, past long-term use of combined oestrogen–progestogen therapy was associated with an increased risk (RR, 1.16; 95% CI, 1.11–1.21), wheras past long-term use of oestrogen-only therapy did not show an increased risk. In terms of absolute risk, oestrogen-only users had between three and eight extra cases of breast cancer per 10,000 women-years; combined MHT users had between nine and 36 extra cases per 10,000 woman-years. No excess breast cancer risk was associated with oestrogen creams or vaginal preparations.[67]

Different results were seen in long-term follow up of two placebo-controlled trials involving 27,347 postmenopausal women aged 50 to 79 years with no history of breast cancer, randomised to receive either CEE plus MPA, CEE alone or placebo. After a median follow up of 20 years, CEE alone in women with a prior hysterectomy (n=10,739) was associated with a lower risk of breast cancer (HR, 0.79; 95% CI, 0.65–0.93; p=0.005) and lower breast cancer mortality (HR, 0.60; 95% CI, 0.37–0.97, p=0.04). In contrast, CEE plus MPA was associated with a higher incidence of breast cancer (HR, 1.28; 95% CI, 1.13–1.45; p<0.001), but without a significant difference in breast cancer mortality.[68] These findings are consistent with those of the WHI.[56]

Endometrial cancer

Women in the oestrogen-alone arm of the WHI study had all undergone hysterectomy.[18] There was no difference in endometrial cancer with combined oestrogen–progestogen compared with placebo (Table 2).[19]

Colorectal cancer

Combined oestrogen–progestogen reduced colorectal cancer compared with placebo.[19] No difference was observed with oestrogen alone compared with placebo (Table 2).[18]

WHI and cardiovascular disease

Coronary heart disease

This was the primary outcome measure of WHI. Early reports of the WHI study described an increased incidence of coronary heart disease (CHD) with combined oestrogen–progestogen compared with placebo, but not with oestrogen alone (Table 2).[19] Post hoc analyses suggested a critical 10-year window after menopause: in women aged 50 to 59 years, there was no increase in CHD in either arm and indeed a nonsignificant trend toward cardioprotection, particularly with oestrogen alone, translating to 11 fewer cases of CHD per 10,000 patient-years.[56] In contrast, an analysis combining the results of both treatment arms of the WHI study showed that MHT initiated more than 10 years after menopause conveyed no

TABLE 2. OTHER OUTCOMES REPORTED FROM THE WOMEN'S HEALTH INITIATIVE STUDY

Outcome	Hazard ratio (95% CI)*	
	Oestrogen alone	Oestrogen–progestogen
Reported results at time of trial cessation[16,17]		
Invasive breast cancer	0.77 (0.59–1.01)	1.26 (1.00–1.59)
Colorectal cancer	1.08 (0.75–1.55)	0.63 (0.43–0.92)
Endometrial cancer	N/A	0.83 (0.47–1.47)
Deep venous thrombosis	1.47 (1.04–2.08)	2.07 (1.49–2.87)
Pulmonary thromboembolism	1.34 (0.87–2.06)	2.13 (1.39–3.25)
Stroke	1.39 (1.10–1.77)	1.41 (1.07–1.85)
CHD	0.91 (0.75–1.12)	1.29 (1.02–1.63)
CHD death	0.94 (0.65–1.36)	1.18 (0.70–1.97)
Non-fatal MI	0.89 (0.7–1.12)	1.32 (1.02–1.72)
Death (total)	1.04 (0.88–1.22)	0.98 (0.82–1.18)
18-year cumulative follow up[68]		
All-cause mortality	0.94 (0.88–1.01)†	1.02 (0.96–1.08)†
Breast cancer mortality	0.55 (0.33–0.92)	1.44 (0.97–2.15)
Colorectal cancer mortality	1.21 (0.79–1.84)	1.01 (0.69–1.49)
Cancer mortality	0.99 (0.86–1.13)	1.06 (0.95–1.18)
Stroke mortality	0.98 (0.77–1.26)	1.12 (0.91–1.38)
CHD mortality	0.89 (0.75–1.05)	1.05 (0.89–1.23)
Cardiovascular disease mortality‡	0.97 (0.86–1.09)	1.03 (0.92–1.15)

Abbreviations: CI = confidence interval; CHD = coronary heart disease; MI = myocardial infarction; N/A = not applicable.
* Nominal rather than adjusted figures from Women's Health Initiative publications are presented.
† In women aged 50 to 59 years, pooled analysis showed a significant reduction in mortality during the intervention phase (HR, 0.69; 95% CI, 0.51–0.94). This reduction in mortality was not significant when menopausal hormone therapy was initiated in older age groups.
‡ Includes deaths due to MI, CHD, stroke, heart failure, peripheral vascular disease, venous thromboembolism and other major causes of cardiovascular disease.

cardiac benefit, with a trend to increased risk.[69]

These conclusions are supported by the Early versus Late Intervention Trial with Estradiol (ELITE), which found that, compared with placebo, oestrogen (plus vaginal progesterone in women with a uterus) reduced the rate of increase of carotid artery intima–media thickness in women in whom MHT was initiated within six years of menopause, but not in those in whom it was initiated more than 10 years after menopause.[70] A Cochrane review also found decreased CHD and lower mortality in women who started MHT within 10 years of menopause.[71]

A systematic review and meta-analysis of 26 RCTs and 47 observational studies conducted between 2000 and 2019 was conducted to assess the association between MHT and cardiovascular disease. Populations in the RCTs were older than in observational studies (median age, 63.6 years *vs* 60.1 years, respectively), and with higher comorbidities at baseline. In most of the RCTs, oral MHT was used, whereas some observational studies used transdermal and vaginal oestrogen. Overall, MHT was not associated with all-cause death (summary estimate [SE], 1.00; 95% CI, 0.96–1.04 in RCTs; SE, 0.90; 95% CI; 0.79–1.02 in observational studies) or cardiovascular death (SE, 0.96; 95% CI, 0.83–1.12 in RCTs; SE, 0.81; 95% CI, 0.61–1.07 in observational studies).[72] In the pooled results, MHT was not associated with myocardial infarction in RCTs, and was associated with a reduced risk of myocardial infarction in observational studies (SE, 0.79; 95% CI, 0.75–0.84), regardless of regimen, timing of initiation or underlying disease at baseline. In a subgroup analysis of observational studies, a decreased risk of all-cause death was observed in oestrogen-only users (SE, 0.85; 95% CI, 0.77–0.95) and early users after menopause (defined as age under 60 years or initiation within 10 years since menopause) (SE, 0.68; 95% CI, 0.51–0.92).[72]

Concerningly, stopping MHT may have adverse cardiovascular consequences. Several studies, including the Women's International Study of Long-Duration Oestrogen after Menopause (WISDOM), were stopped prematurely because of the WHI publications. A Finnish study found that there was an increased risk of cardiac death in women aged under 60 years in the year after MHT discontinuation (standardised mortality ratio [SMR], 1.52; 95% CI, 1.13–2.00 after less than or equal to five years' exposure; SMR, 2.08; 95% CI, 1.44–2.90 after more than five years' exposure).[73]

Pulmonary thromboembolism and deep venous thrombosis

Pulmonary thromboembolism (PTE) and deep venous thrombosis (DVT) are increased with some forms of MHT. In the WHI study, DVT and PTE were increased with combined oestrogen–progestogen, with an absolute risk of eight additional PTEs per 10,000 patient-years and with the greatest risk in the first two years of use.[19] With oestrogen alone, only the increase in DVT reached statistical significance; the increase in PTE risk was not significant (Table 2).[18] In the systematic review and meta-analysis discussed above, oral oestradiol was associated with increased risk of VTE in both

RCTs (SE, 1.70; 95% CI, 1.33–2.16) and observational studies (SE, 1.32; 95% CI, 1.13–1.54), especially in combined oestrogen–progestogen users, late users (more than 10 years after menopause) and women with underlying comorbidities at baseline. PTE risk was also increased with MHT use in both RCTs (SE, 1.26; 95% CI, 1.06–1.50) and observational studies (SE, 1.44; 95% CI, 1.17–1.76).[72]

Stroke

Stroke was increased in both treatment arms of the WHI study, compared with placebo, amounting to an absolute risk of 12 additional strokes per 10,000 person-years in the oestrogen-alone arm and eight in the combined treatment arm (Table 2). Stroke risk was not affected by time since menopause at time of MHT initiation. Extended follow up has not shown any increase in stroke mortality.[66] In a pooled analysis of predominantly oral MHT, MHT was associated with increased risk of stroke in RCTs (SE, 1.14; 95% CI, 1.04–1.25) but not in observational studies (SE, 0.98; 95% CI, 0.85–1.13). In subgroup analyses of RCTs, increased risk of stroke was associated with combined oestrogen-progestogen use, MHT duration greater than five years, late users after menopause, and in those with underlying cerebrovascular disease at baseline. In subgroup analyses of observational studies, decreased stroke risk was observed in women administered nonoral MHT (SE, 0.86; 95% CI, 1.04–1.18).[72]

Does the type of oestrogen or oestrogen–progestogen matter for CHD risk?

Oral oestrogens increase clotting factors and inflammatory markers, an effect not seen with transdermal oestrogen, which bypasses first-pass hepatic metabolism.[74,75] Observational studies have suggested reduced risks of cardiovascular disease (CVD), stroke and PTE with transdermal compared with oral oestrogen preparations.[76-79] However, this has not been assessed in head-to-head studies.

The promiscuity of progestogen binding to multiple receptor types, with differing affinity and action (agonist *vs* antagonist effects), can result in quite different risk profiles for different progestogens, which may include CVD risk. However, this is conjectural, and the contribution of progesterone to thrombogenesis is unknown.

It is important to note that the WHI study used oral CEE and medroxyprogesterone acetate, and most women were more than 10 years post menopause, with an average age of 63 years. This does not reflect current prescribing practices which includes lower-dose oestrogens, transdermal oestrogens and newer progestogens including localised delivery (e.g. placement of a hormonal intrauterine device), with prescribing predominately in younger women.[80]

Additional side effects of oestrogen–progesterone

A recent analysis of pooled data from 20 trials (n=39,145) and three cohort studies (n=1,155,410) assessed the effects of oestrogen-only and combined oestrogen–progestogen therapies. Oestrogen-only therapy was associated with lower rates of diabetes (134 per 10,000 persons) and fractures (388 fewer per 10,000 persons) compared with placebo, but higher rates of gallbladder disease (377 per 10,000 persons), stroke (79 per 10,000 persons), venous thromboembolism (VTE; 77 per 10,000 persons) and urinary incontinence (885 per 10,000 persons).[81] Combined oestrogen–progestogen was associated with lower risk of colorectal cancer (34 per 10,000 persons), diabetes (78 per 10,000 persons) and fractures (230 per 10,000 persons), but increased risks for invasive breast cancer (51 per 10,000 persons), gallbladder disease (260 per 10,000 persons), stroke (52 per 10,000 persons) and VTE (120 per 10,000 persons). Additionally, combined oestrogen–progestogen therapy was associated with a probable increased risk of dementia (88 per 10,000 persons) and urinary incontinence.[82] However, there is conflicting evidence regarding the impact of MHT use on dementia risk. Specifically, among women with the *APOE* gene (associated with Alzheimer's disease risk) in the European Prevention of Alzheimer's Disease (EPAD) cohort, those using MHT showed improvement in delayed memory stores and increased hippocampal volumes compared with non-users.[82]

Side effects of SERMs, TSECs and tibolone

Both raloxifene and lasofoxifene reduce the risk of breast cancer.[32,34] Preclinical evidence suggests bazedoxifene may also reduce risk of breast cancer.[83,84]

SERMs increase risk of thromboembolism (both DVT and PTE).[32,34,85] An increased risk of thromboembolic disease has not been reported with tibolone.[37]

Raloxifene increases the risk of fatal but not overall stroke (HR, 1.49; absolute risk of seven more cases per 10,000 women).[86] In contrast, lasofoxifene reduces the risk of stroke.[34] Tibolone is associated with increased stroke risk in older women.[37]

Overall, raloxifene does not reduce coronary artery disease, although the Raloxifene Use for The Heart (RUTH) study (in women with established CHD or risk factors for CHD) suggested a protective effect in women aged under 60 years (p for interaction of age with coronary artery disease: 0.01).[32,87] Lasofoxifene reduces CHD at higher (0.5 mg) but not lower (0.25 mg) daily doses.[34]

SERMs may worsen vasomotor symptoms, whereas TSECs may reduce them. Tibolone is less effective than oestrogen or oestrogen–progestogen for vasomotor symptoms.[88]

Clinical indications for MHT use for bone health

There are many guidelines regarding use of MHT.[89-91] Generally, there is concordance that MHT is appropriate and effective for vasomotor symptoms, assuming no contraindications.[92] There is much less consensus regarding the use of MHT primarily for prevention or treatment of osteoporosis, particularly as a first-line agent, and questions regarding age of initiation, duration and monitoring of MHT are largely unanswered. Updated recommendations and guidelines for MHT use for bone health are summarised in Table 3.[26,28,89-91,93,94]

Recommendations for MHT use: update since 2019

Recommendations on MHT use for women with postmenopausal osteoporosis continue to vary among organisations. The 2022 US Preventative Services Task Force (USPSTF) guidelines still currently recommend against combined oestrogen–progestogen, or oestrogen alone (in postmenopausal women, for the prevention of chronic conditions, including osteoporosis), concluding a lack of net benefit.[91] The American Association of Clinical Endocrinologists/American College of Endocrinology Practice Guideline 2020 update also still recommends that MHT only be

TABLE 3. GUIDELINES AND RECOMMENDATIONS FOR USE OF MHT FOR BONE HEALTH

Source	Year	Recommendations	Use of MHT specifically for bone health
American College of Physicians (ACP)[16]	2023	• No specific recommendation on MHT for postmenopausal osteoporosis • The ACP recommends bisphosphonates be used for initial pharmacological treatment to reduce risk of fractures in women with osteoporosis	X
Healthy Bones Australia[28]	2023	• Consider MHT for younger postmenopausal women if initiated within 10 years of menopause and under the age of 60 years, particularly if they have troublesome menopausal symptoms	✓
US Preventive Services Task Force[91]	2022	• Recommendation against MHT for primary prevention of chronic conditions including osteoporosis due to lack of net benefit	X
North American Menopause Society[89]	2021	• The primary indication for systemic hormone therapy is for the relief of vasomotor symptoms in postmenopausal women aged younger than 60 years and within 10 years of menopause, with secondary benefit on bone protection. However, can be considered in women with persistent menopause symptoms and those at high risk of fracture who cannot tolerate other therapies if benefit outweighs the risk • Despite positive effects on bone, initiating MHT in women older than 60 years or after more than 10 years of menopause is not recommended due to concerns about cardiovascular safety	✓ (Second-line only)
American Association of Clinical Endocrinologists and American College of Endocrinology[26]	2020	• The use of MHT should be considered for women at significant risk of osteoporosis, in whom nonoestrogen medications are inappropriate, and that when used for the relief of menopausal symptoms oestrogen be prescribed at the lowest dose and for the shortest time possible	✓ (Second-line only)
Global consensus statement*[93]	2016	• MHT (including tibolone and CEE–bazedoxifene) is effective in preventing bone loss and hip, vertebral and other osteoporotic fracture in postmenopausal women • MHT is the only therapy available with RCT-proven fracture reduction in postmenopausal women not selected for risk of fracture and with mean T-scores in the normal to osteopenic range • MHT can be initiated in postmenopausal women at risk of fracture or osteoporosis before the age of 60 years or within 10 years after menopause • 'Consideration of MHT for symptom relief or osteoporosis prevention should be part of an overall strategy' • Initiation of MHT after the age of 60 years for fracture prevention is considered second-line therapy and requires individual risk–benefit assessment	✓
European Menopause and Andropause Society[94]	2015	• MHT is the most effective treatment for vasomotor symptoms, and benefits are more likely to outweigh risks for symptomatic women before the age of 60 years or within 10 years after menopause; the benefits are not specifically defined • MHT can be continued for up to five years and then reassessed, but there is no arbitrary limit regarding the duration of use • Oestrogen-based therapy is the treatment of choice for women under the age of 60 years or within 10 years of menopause for reducing the risk of osteoporotic fracture	✓

Abbreviations: CEE = conjugated equine estrogens; MHT = menopausal hormone therapy; RCT = randomised controlled trial.
* Endorsed by the Federation of Latin American Menopause Societies, Asia Pacific Menopause Federation, Endocrine Society, European Menopause and Andropause Society, International Menopause Society, International Osteoporosis Foundation and North American Menopause Society.

considered for women who are at significant risk of osteoporosis and in whom nonoestrogen medications are inappropriate, and that if used for relief of menopausal symptoms, oestrogen be prescribed at the lowest dose and for the shortest time possible.[26]

However, the 2022 Hormone Therapy Position Statement of the North American Menopause Society recommends risk stratification by age and time since menopause, and consider that the benefits of MHT outweigh the risks in most healthy women with vasomotor or genitourinary symptoms younger than 60 years and within 10 years of the onset of menopause for the prevention of bone loss.[89] Similarly, a revised Global Consensus Statement on Menopausal Hormone Therapy, endorsed by several international organisations, including the International Menopause Society, The North American Menopause Society, the Endocrine Society and The International Osteoporosis Foundation, recommends MHT for the prevention of bone loss in most healthy symptomatic women younger than 60 years and within 10 years of menopause onset.[93] Healthy Bones Australia 2023 guidelines suggest MHT as an option for young postmenopausal women, if initiated within 10 years of menopause or under 60 years of age, particularly for women with troublesome menopausal symptoms.[28]

Monitoring during MHT use for osteoporosis

There are no specific monitoring requirements for MHT used for bone health (e.g. BMD follow up), as opposed to general comments regarding MHT use for treatment of menopausal symptoms. Local guidelines should be consulted.

MHT contraindications and adverse side effects

The North American Menopause Society 2022 position statement recommends the following as contraindications to oral and transdermal MHT: unexplained vaginal bleeding, liver disease, prior oestrogen-sensitive (including breast) cancer, CHD, stroke, myocardial infarction, VTE and personal history or inherited risk of VTE. Observational studies have not demonstrated an increased risk of thromboembolic risk with transdermal oestrogen (see below) and some practitioners consider transdermal therapy can be used with caution in women with a past history of stroke or transient ischaemic attack, myocardial infarction, gall bladder disease and hypertriglyceridaemia.[95] Adverse effects that should be discussed with women considering MHT are nausea, bloating, weight gain, fluid retention, mood swings, breakthrough bleeding, worsening migraines, leiomyoma growth and exacerbation of endometriosis.[89] Furthermore, modern guidelines do not recommend placing an upper limit on the duration of MHT use, particularly where there is ongoing benefit.[89,94,96]

Cessation of MHT

After cessation of MHT, cardiovascular risk will increase; this is often forgotten. Rapid bone loss will also ensue after cessation, as is observed after natural menopause. Alternative osteoporosis-specific treatment should be offered to women at high risk of fracture.

Conclusion

Use of MHT is justified in its own right for treating distressing vasomotor symptoms (discussed in multiple societal guidelines listed in Table 3).

MHT improves BMD and reduces fracture risk in women across the BMD spectrum, as seen in the WHI trial. However, the absolute benefit of treatment will be greater in women at higher risk of fracture (e.g. BMD T-score less than –2.5, or previous fracture). The use of MHT for the sole indication of primary prevention of osteoporosis in all postmenopausal women, irrespective of BMD, seems excessive. However, shutting the stable door before the proverbial horse has bolted is a reasonable concern for many women.

MHT is a valid option for younger postmenopausal women within 10 years of cessation of menses who have osteopenia or osteoporosis by BMD criteria, or previous minimal trauma fracture, and without specific contraindications. However, it should be noted that women with previous fracture are eligible for other agents to treat osteoporosis (albeit with their own long-term side effects) and that absolute fracture risk at this young age, even in women with low BMD, is low.

Notwithstanding the above, the influence of the WHI study is such that many women are fearful of MHT due to continuing overemphasis of the risks, and many doctors are reluctant to prescribe it. Ongoing education of the wider medical community regarding the limitations of the WHI study will enable practitioners to prescribe MHT with more confidence. As with any medication, prescribing MHT requires an informed discussion about risks versus benefits. These vary from woman to woman and include age, time since menopause, other risk factors for fracture (e.g. previous fracture) and other risk factors for CVD (e.g. smoking). The choice of MHT preparation should be tailored to the individual patient's clinical profile and preference. Transdermal therapies confer a lower risk of CVD than oral preparations.

Optimal duration of MHT is unclear and modern guidelines do not recommend an upper limit on the duration of use. Whether the adverse consequences of treatment observed in women initiating MHT at an older age apply to women who start MHT in the immediate postmenopausal period and continue use to this same age is unknown. As a rule of thumb, many endocrinologists would consider initiating, and continuing, MHT until the age of 60 years. The decision to cease MHT is an individual one, and many women may choose to continue treatment beyond this age for various reasons, including improved quality of life. After cessation of MHT, management of cardiovascular risk and fracture risk will need re-evaluation. MT

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Postmenopausal osteoporosis

Is there a role for menopausal hormone therapy?

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Menopause management after breast cancer

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Increasing breast cancer incidence and decreasing mortality have highlighted the importance of survivorship issues related to breast cancer. Management of menopause in breast cancer survivors is complex and menopausal symptoms should be treated to enhance quality of life and long-term health.

Breast cancer is the most common cancer affecting women in Australia. It was estimated that 20,640 women would be diagnosed with breast cancer in 2022.[1] Despite the high incidence of breast cancer, survivorship is high. The most recent statistics show that the five-year relative survival rate for women diagnosed with breast cancer in in 2013 to 2017 was 92%.[2]

As the number of breast cancer survivors increases, menopause has become an increasingly important issue for women who have had a breast cancer diagnosis. Most women diagnosed with breast cancer are postmenopausal, as are most survivors.[3] Further, premenopausal women diagnosed with breast cancer often experience early menopause because of breast cancer treatments.[4]

Management of menopause in women after breast cancer is complex, and menopausal symptoms can negatively affect quality of life and have potential long-term health impacts. Menopause symptoms are often more severe after breast cancer treatment – especially in women who become postmenopausal as a result of their treatment – and due to a paucity of effective treatment options, since menopausal hormone therapy (MHT; formerly known as hormone replacement therapy or HRT) is usually contraindicated. Common problematic symptoms of menopause are broadly classified as vasomotor, genitourinary and sexual dysfunction, and mood symptoms. Osteoporosis and cardiovascular disease are potential longer-term consequences related to menopause.

A multidisciplinary approach including breast cancer specialists, and possibly a menopause specialist, with the GP overseeing – if they are comfortable treating the menopausal symptoms – is recommended for treating menopause in women after a breast cancer diagnosis.[5]

Causes of menopausal symptoms

In women who have had a past diagnosis of breast cancer, bothersome menopausal symptoms may be associated with:

- natural menopause occurring concurrently with a breast cancer diagnosis
- recurrence of menopausal symptoms after cessation of MHT when breast cancer is diagnosed
- chemotherapy
- endocrine adjuvant therapy with tamoxifen or aromatase inhibitors (AIs)
- ovarian suppression secondary to gonadotrophin-releasing hormone (GnRH) agonists in premenopausal women
- risk-reducing bilateral oophorectomy.

Most breast cancers are estrogen receptor (ER) positive and the use of endocrine adjuvant therapy, by inducing oestrogen deprivation, improves disease-free survival. Tamoxifen acts as an ER antagonist in breast tissue with partial agonist effects on the endometrium, bone and vagina. AIs inhibit conversion of androgens to oestrogens, thereby reducing serum estradiol levels

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to below those seen in healthy postmenopausal women (<20 pmol/L). Among premenopausal women on chemotherapy for breast cancer, amenorrhoea leading to menopause is induced in up to 80% and increased risk of permanent amenorrhoea is observed with older age, longer duration of treatment, type of chemotherapy regimen and tamoxifen use.

Symptoms

Multiple factors influence menopause symptomatology, including age, type of menopause, lifestyle, comorbidities, demographic characteristics and psychosocial factors. Thus, the individual menopause experience may vary widely.

Vasomotor symptoms are reported by up to 95% of breast cancer survivors and are more severe compared with those reported by women without cancer.[6] Genitourinary symptoms such as vaginal dryness occur commonly in women with breast cancer, with 50 to 75% of breast cancer survivors reporting one or more symptoms.[7] Sexual dysfunction is common in women with breast cancer, affecting up to 70% of breast cancer survivors.

Menopausal symptoms are more frequent and severe in younger women with treatment-induced menopause compared with older women with breast cancer.[6] However, it can be difficult to distinguish between the effects of breast cancer treatments (joint aches and muscle pains are common symptoms in women taking AIs), menopause and ageing.

Cardiovascular disease and osteoporosis risk

Cardiovascular disease (CVD) and breast cancer share risk factors such as obesity and inactivity, as well as increased incidence in women aged over 50 years.[3] Hypertension is the most common comorbidity across all age groups of breast cancer survivors, and affects up to 50% of those aged over 65 years. CVD is the third most common comorbidity across all age groups.[3]

Bone loss and fractures in women who have had a diagnosis of breast cancer may result from:

- direct or systemic effects of the tumour[5]
- oestrogen deprivation leading to induced early menopause secondary to breast cancer therapies (i.e. chemotherapy, ovarian ablation or AIs)
- natural menopause and/or other secondary causes of bone loss such as corticosteroids.

The highest rates of bone loss (7 to 8% per year at the lumbar spine) are observed in premenopausal women treated with chemotherapy or GnRH suppression plus AIs.[8]

Vasomotor symptoms are reported by up to 95% of breast cancer survivors and are more severe compared with those reported by women without cancer

Case scenario

Maria is a 45-year-old premenopausal woman with no family history of breast cancer. She presents to her GP for her breast check and cervical screen and a left breast lump is found on examination, which she was unaware of.

A mammogram and ultrasound show a suspicious 1 cm lesion in the left breast. Biopsy specimens show an intraductal carcinoma that is ER positive, progesterone receptor positive and HER2 negative.

Maria undergoes wide local excision of her breast cancer. One sentinel node is removed, which is negative.

She is advised to undergo radiotherapy and then to take tamoxifen orally. After starting tamoxifen, her periods become irregular and she experiences hot flushes and sweats, which impact on her quality of life. She is tired, has aches and pains, loss of libido and dyspareunia. She feels anxious and depressed and is worried about a cancer recurrence.

Management approach

Evaluation of menopausal symptoms

A very clear history of the symptoms and their impact on Maria's quality of life is needed, including the type, frequency, severity and impact of symptoms, and she should be asked to prioritise which symptoms have the most impact on her quality of life. Likely causes and triggers of symptoms should be identified, as well as what Maria hopes for from the treatment intervention. Vasomotor, genitourinary and sexual dysfunction symptoms and mood symptoms such as anxiety, depression and fear of recurrence are treated individually (see management strategies for specific menopausal symptoms below). Maria can be further supported with psychological support and education and referral to websites that have evidence-based information.

Lifestyle modification

Lifestyle modifications that may improve symptoms can be recommended. As relevant, Maria should be encouraged to stop smoking, maintain a healthy weight, limit alcohol intake, eat healthily and undertake daily physical activity.

CVD risk assessment

Cardiac risk factors need to be identified, including smoking, family history, depression, physical inactivity, body mass index (BMI) and blood pressure. Diabetes and lipid status also need to be determined.

Osteoporosis risk assessment

It is important to also identify osteoporosis risk factors, including age, BMI of less than 20 kg/m^2, family history of hip fracture, personal history of fragility fracture, smoking or use of corticosteroids for more than six months. Adequate calcium and vitamin D levels should be ensured. If the woman has risk factors for osteoporosis, consider referring her for bone density scanning (dual-energy x-ray absorptiometry) to help in the decision-making process. (This will have

already been performed if she is being treated with an aromatase inhibitor.)

Management strategies for specific menopausal symptoms

Vasomotor symptoms

Managing hot flushes and night sweats through lifestyle modification can be recommended. Dressing in layers and using fans and water sprays may help these symptoms.

Medication options include use of a selective serotonin reuptake inhibitor (SSRI; e.g. escitalopram) or a serotonin and noradrenaline reuptake inhibitor (SNRI; e.g. venlafaxine), gabapentin, clonidine or oxybutynin, all of which are used 'off label'. Review the patient after four to six weeks and if there is no effect or she cannot tolerate the medication, then change to another nonhormonal agent. If there is still intolerance or no effect then discuss changing or suspending adjuvant therapy with the oncology team.

Note that some nonhormonal treatments with some SSRIs (fluoxetine and sertraline, but particularly paroxetine) should not be used with tamoxifen. It is possible to use a combination of an antidepressant and gabapentin if necessary for control of symptoms. These therapies usually provide a symptom response within four weeks. Nonpharmacological interventions such as cognitive behavioural therapy and hypnotherapy can also be considered. Current safety data do not support the use of MHT in breast cancer survivors. Only after all other options have failed, and after counselling and discussion with the woman's breast treatment team, a trial of MHT might be considered.

Genitourinary symptoms

Genitourinary symptoms can include vaginal dryness, loss of lubrication during sex, pain with sex, urinary urgency, urge incontinence and recurrent urinary infections. Lifestyle changes can be encouraged, including stopping smoking, addressing perineal hygiene and, if sexually active, regular sex. Regular use of vaginal moisturiser should be recommended.

If genitourinary symptoms persist, then consider a trial of vaginal estriol or estradiol preparation, or changing adjuvant therapy after consultation with the breast cancer team. Any dermatological problem or infection should be excluded and regular use of lubricant with vaginal intercourse encouraged.[9] Vaginal laser treatment has been promoted for vaginal dryness, but the studies at present are only short term and not placebo controlled.

Only after all other options have failed, and after counselling and discussion with the woman's breast treatment team, a trial of MHT might be considered

Sexual dysfunction

If Maria's sexual function is impaired, the pelvic floor should be examined for pain and tenderness. Consider referral to a pelvic floor physiotherapist for dyspareunia and overactive pelvic floor, and use of a vaginal dilator. Medications that are having a negative impact on sexual function need to be identified and changed. If necessary, refer Maria for psychosocial intervention, including couple counselling, sexual counselling, cognitive behavioural therapy and education from evidence-based websites.

Mood symptoms

Adjusting to the diagnosis of breast cancer as well as experiencing all of the treatments is often traumatic. When menopause occurs as a consequence of the treatments, dealing with menopause symptoms can be overwhelming and may lead to anxiety, mood swings and depression. Referral to a psychologist or counsellor may be helpful.

Conclusion

Increasing breast cancer incidence and decreasing mortality have highlighted the importance of survivorship issues related to breast cancer. Management of menopause in breast cancer survivors is complex and a multidisciplinary approach is considered the best approach for the successful management of vasomotor, genitourinary and sexual dysfunction symptoms, and prevention of osteoporosis and cardiovascular disease. Management of menopausal symptoms involves evaluation, individualised treatment of specific symptoms, psychological support and education. Lifestyle modification may help both symptoms and the longer-term consequences of menopause. MT

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