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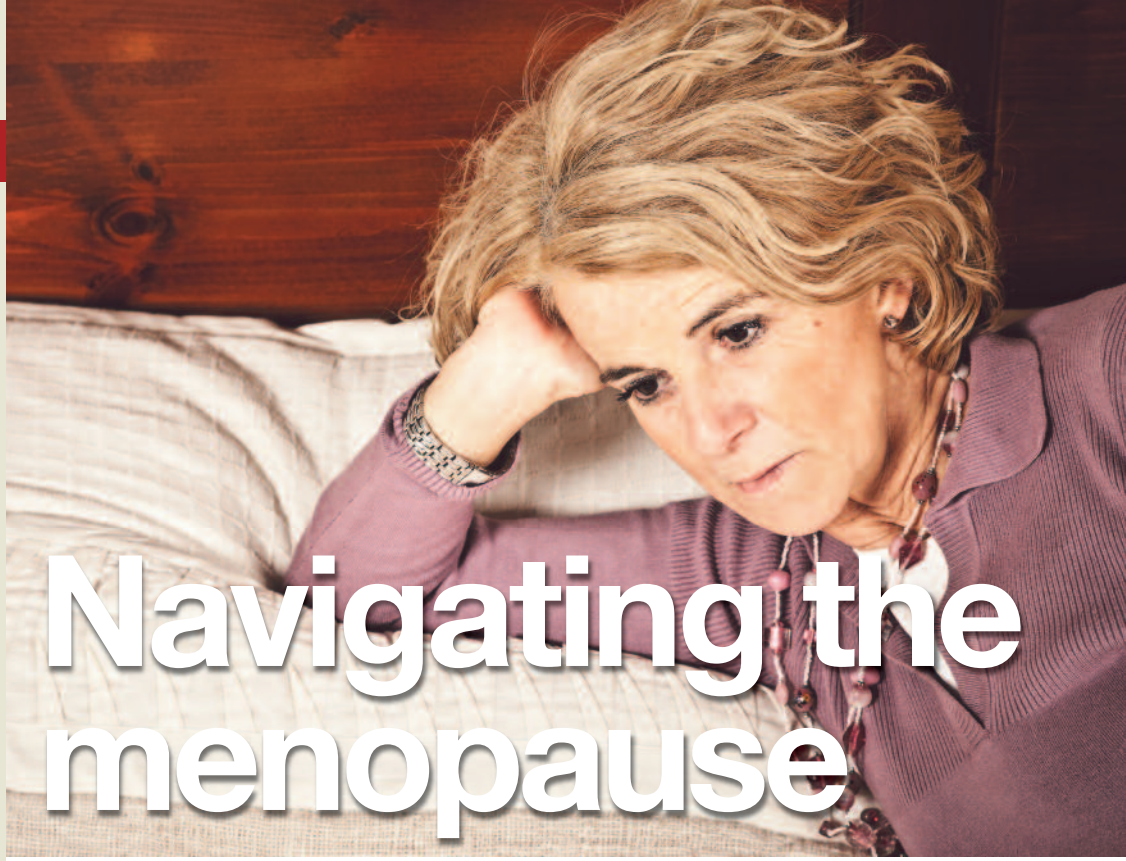

Navigating the menopause

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During or after the menopause transition, women may present with a constellation of mild to severe symptoms. Treatment is intended to alleviate symptoms that impair quality of life and to optimise health and wellbeing.

Key points

- Women may present during or after the menopause transition with problems such as menstrual irregularity, hot flushes and night sweats, change in sleep quality, depression and anxiety, arthralgia and symptoms of urogenital atrophy.
- Diagnosis of natural meno - pause is based on change in menstrual flow and eventually amenorrhoea, with the last menstrual period being the date of menopause. It is a retrospective diagnosis after 12 months of amenorrhoea.
- Diagnosis of premature ovarian failure requires oestradiol and gonadotrophin levels to be measured.
- Hormone levels are not informative for diagnosing menopause in women using systemic combined contra - ception but may be useful for women who have had a hysterectomy or endometrial ablation or have a progestin intrauterine device in situ.
- Treatment goals for the menopausal woman are to alleviate symptoms that impair quality of life and to optimise health and wellbeing.

Menopause is the permanent cessation of menses following the loss of ovarian follicular activity. The loss of ovarian oestrogen production results in physical symptoms, especially vasomotor symptoms, which may be debilitating, as well as menopause-specific depression, sexual dysfunction, bone loss and metabolic changes that predispose to cardiovascular disease and diabetes. The menopause transition, or perimenopausal period, commences with variation in the length of the menstrual cycle and, by definition, ends after 12 months of amenorrhoea, with natural menopause mostly occurring between the ages of 45 and 54 years. The goals of treatment are to alleviate symptoms that impair quality of life and to optimise health and wellbeing, including addressing issues such as prevention of bone loss, cardiovascular disease and diabetes.

DEFINITIONS

Natural menopause is the last menstrual period in a woman who has not had a hysterectomy, diagnosed after 12 months of amenorrhoea.

In a woman who has had a hysterectomy or endometrial ablation or has a progestin intrauterine device in situ, menopause can be harder to diagnose. After menopause, the level of follicle stimulating hormone (FSH) will be elevated and the level of oestradiol will be low, but during the perimenopause these hormone levels fluctuate and may not be helpful for diagnosis. Determining the menopausal status of a woman who is using a systemic combined contraceptive (oral contraceptive pill or vaginal ring) requires her to cease the contraceptive before clinical review.

Surgical menopause refers to menopause induced by removal of both ovaries before natural menopause.

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Premature ovarian failure is defined as menopause occurring before the age of 40 years. Premature ovarian failure affects 0.1% of women by the age of 30 years and 1% of women by the age of 40. It is not permanent in all women.

Perimenopause describes the time from when menses become irregular until 12 months after the last menstrual period, such that the menopause transition begins with variation in menstrual cycle length and ends after 12 months of amenorrhoea.

Postmenopause is the term applied when a woman has not experienced a menstrual bleed for at least 12 months.

PHYSIOLOGY OF THE MENOPAUSE

Hormonal changes during the perimenopause

The young ovary consists of incompletely developed ova encased by the supportive oestrogen-producing follicular cells. The number of immature ova drops from 7.5 million in a healthy 20-week-old fetus to 2 million at birth and to 300,000 at puberty; the rate of loss accelerates at about 37 years of age, when the number of healthy ova has decreased to about 25,000. Menopause occurs when there is extensive deterioration of the follicular cells and immature ova, and blood levels of oestrogen and progesterone fall, at the average age of 51.7 years.[1] Women at this time may experience symptoms of oestrogen insufficiency.

When the integrity of the ovarian follicular cells deteriorates, the oestradiol level begins to fall, and this change is detected by both the hypothalamus and the pituitary gland. In addition, ovarian production of the protein inhibin diminishes. The pituitary gland responds by producing greater amounts of both FSH and luteinising hormone (LH) in an attempt to drive ovarian function. Thus, as menopause approaches, blood levels of inhibin decline and levels of FSH and LH rise. Serum oestradiol levels fluctuate erratically across the cycle and may increase approaching menopause, with oestradiol production well preserved until late perimenopause.[2]

Anti-Müllerian hormone (AMH), which is produced by developing follicles, may also be used as a marker of declining follicular reserve, and hence menopause. AMH concentrations are relatively stable across the menstrual cycle but decline with age. Nonetheless, there is substantial variation in levels between individuals, and a single measurement is not informative about the rate of decline in an individual. Although a low AMH level is highly suggestive of ovarian failure, it is not conclusive. Importantly, AMH concentrations at any given age appear to mirror primordial follicular recruitment rates, rather than simply primordial follicle number, limiting their clinical usefulness. For example, in the setting of quiescent ovarian function, such as hypothalamic amenorrhoea, when follicles are not being recruited, AMH levels may be very low yet the diagnosis is not premature ovarian failure.

Predicting age at menopause

The best predictor of the age at which a woman will experience menopause is the age at which her mother or a sister went through menopause.[3] Factors associated with the likelihood of an earlier menopause include cigarette smoking, hysterectomy and a family history of early menopause.

Hormonal changes after menopause

Oestrogen production relies on conversion of androgens to oestrogens by the aromatase enzyme. Before menopause, the ovaries are the main site of oestrogen production. After menopause, oestradiol and oestrone are produced primarily in extragonadal tissues such as adipose tissue, bone, vascular endothelium and aortic smooth muscle cells, and even numerous sites in the brain.[4] Within these sites, aromatase action can generate high local levels of oestradiol and oestrone, and circulating levels of oestrogens in postmenopausal women reflect 'spillover' into the circulation from these tissues.

In contrast to the fall in oestradiol after natural menopause, levels of total and free testosterone, as well as dehydroepiandrosterone sulfate and androstenedione, decline gradually with age.[5] However, women who have had their ovaries surgically removed or damaged by chemotherapy and those with ovarian gonadotrophin suppression will experience significant loss of ovarian androgen production.

DIAGNOSIS OF MENOPAUSE

For women with an intact uterus the menopause transition is diagnosed clinically by a change in the bleeding pattern and eventually amenorrhoea. This is the basis for the stages of the menopause transition in naturally menopausal women not using exogenous hormones, as defined by the Stages of Reproductive Aging Workshop (STRAW).[6] The STRAW stages of menopause are:

- early menopause transition, with variable menstrual cycle length and increased FSH level
- late menopause transition, with periods of amenorrhoea of 60 days or longer and increased FSH level
- early postmenopause, the period up to six years from the final menstrual period
- the late postmenopause, the period beyond this.

In women who cannot report their menstrual pattern because of prior hysterectomy or endometrial ablation, menopause may be diagnosed by hormonal measurement, as previously described. However, to determine whether a woman in her late 40s or early 50s who is using a systemic combined contraceptive is menopausal, have her cease the contraceptive and evaluate her after six to eight weeks for recurrence of natural menses or menopausal symptoms.

INVESTIGATIONS

The laboratory finding that confirms menopause is an elevated FSH level in the setting of a low oestradiol level. However, in the early menopause transition, serum FSH and oestradiol levels may be erratic. Specific cut-off levels vary considerably between laboratories, according to the assays used.

Biochemical testing is required only for women who cannot describe their underlying cycle and younger women with amenorrhoea in whom the differential diagnosis may include hyperprolactinaemia or exercise- or weight loss-induced amenorrhoea.

The diagnosis of premature ovarian failure in women younger than 40 years requires at least four months of amenorrhoea and two to three serum FSH values greater than 40 mIU/mL, obtained at least one month apart.

CLINICAL PRESENTATION OF MENOPAUSE

Menstrual irregularity is considered to be the earliest indication of the menopause transition.[7] Because of the hormone fluctuations during the perimenopause, women may experience intermittent symptoms. These range from hot flushes and night sweats when oestradiol levels fall, through to tenderness and swelling of the breasts and heavy or irregular bleeding when oestradiol levels rise in response to the FSH drive.

Women may experience no menopausal symptoms, or several (see the box on this page). Symptoms may start a number of years before menopause, even when periods are regular, because of variable hormone levels. Across the menopause transition:

- one in four women experience severe vasomotor symptoms (hot flushes and night sweats)
- one in three experience severe psychological symptoms (depression or anxiety)
- one in two women report moderate to severe somatic symptoms (sleep disturbance, joint pain or headache)
- at least one in four women have sexual problems.[8,9]

Symptom duration and impact

Symptoms may last for a few years to, in some women, many years, with 10% having symptoms for more than 10 years. A recent study indicated that women who have minimal vasomotor, psychological, somatic or sexual discomfort symptoms around the time of menopause are unlikely to develop severe symptoms later and, without intervention, the severity of somatic symptoms remains fairly static across the menopause.[8] Importantly, women with moderate to severe menopausal symptoms are likely to have them for several years. Women who experience severe symptoms up to three years before the menopause appear most likely to experience a reduction in symptoms by their fourth postmenopausal year, whereas women with later onset severe vasomotor symptoms appear more likely to have symptoms persist for many years.

Menopausal symptoms, both psychological and somatic, have been reported to account for as much as 36% of the variability in how well a woman is able to perform in the workplace.[10] Considering that 79% of women aged 45 to 54 years are in paid employment (versus 47% in 1980),[11] the hormonal changes experienced by women at menopause have serious socioeconomic consequences.

Vasomotor symptoms

Vasomotor symptoms are the most common presenting symptoms,[7] occurring in almost 80% of women, with 25% reporting these symptoms as severe.[12,13] Vasomotor symptoms are also more common in smokers, in women with greater body mass and after surgical menopause.[14]

Typically, hot flushes are characterised by increased peripheral blood flow, increased heart rate, skin conductance and sweating, and occasionally nausea. The mechanism underlying flushes is not known but may in part involve a change in autonomic function, with recent studies suggesting that the parasympathetic branch of the autonomic nervous system has a role.[15]

Sleep changes

Fragmented sleep and diminished sleep quality are a hallmark of menopause, and are more common among women with vasomotor symptoms, although disturbed sleep architecture can occur independently of these symptoms. The three forms of sleep disorders associated with menopause are:

- insomnia and depression
- sleep disordered breathing
- fibromyalgia.[16]

EFFECTS OF OESTROGEN DEFICIENCY

Commonly reported menopausal symptoms

- Hot flushes and night sweats
- Crawling sensations on skin
- Anxiety and irritability
- Sleep disturbances
- Lessened memory and lessened concentration
- Vaginal dryness
- Low libido
- Arthralgia
- Overall diminished wellbeing
- Depression

Important physical consequences

- Bone loss due to increased bone resorption
- Central abdominal weight gain
- Conversion to a more adverse cardiovascular risk lipid profile
- Stress and urge urinary incontinence
- Vaginal atrophy

ASSESSMENT OF A WOMAN AT MENOPAUSE

- Current health
- Lifestyle: diet (calcium, iron, vitamin D intake), smoking, alcohol, exercise
- Medications, including nonprescribed therapies
- A full medical history:
  - oral contraceptive use, migraines*
  - past thrombosis
  - cardiovascular risk, fractures, breast lumps
  - family history of disease
  - psychological, social and sexual histories
- A thorough medical examination

* A history of migraines related to the menstrual cycle or oral contraceptive use would influence the use and mode of hormone therapy. Referral to a specialist should be considered.

The mechanism underlying the change in sleep pattern is not known, but treatment of insomnia may be an important indication for hormone therapy.

Depression

Depression is a menopausal symptom experienced by many women. Women with a history of depression are nearly five times as likely to be diagnosed with depression during the perimenopause,[17] and women with no history of depression are two to four times more likely to be diagnosed than premenopausal women.[18] Premenstrual syndrome is a strong predictor of perimenopausal depression.[19]

Perimenopausal depression is characterised by a different constellation of symptoms to depression emerging at other life stages, with consequences for diagnosis and management. Diagnosis of a major depressive episode requires at least two weeks of depressed mood or loss of interest or pleasure in nearly all activities most of the day, nearly every day, accompanied by at least four of the following symptoms: change in appetite or sleep, fatigue, psychomotor agitation or retardation, feelings of worthlessness or guilt, diminished concentration, or indecisiveness and suicidal ideation.

In contrast, perimenopausal depression presents as dysphoric mood, characterised by feeling depressed, irritable, hostile, tense or nervous.[20] Clinically it resembles the mood changes of premenstrual syndrome, with negative mood, negative self-concept, irritability and less effective coping abilities. Another distinguishing feature is that perimenopausal depression is highly labile, unlike the pervasive low mood seen in major depression.

Perimenopausal depression needs to be differentiated from a major depressive episode or dysphoria, as the optimum management approach differs between these conditions. Perimenopausal depression is likely to respond to hormone therapy, and less likely to respond to antidepressant therapy.

Arthralgia

Arthralgia is a common menopausal symptom that occurs with increasing frequency as women progress though the menopausal stages, in association with increasing FSH levels.[21] The strongest evidence that arthralgia is a consequence of oestrogen depletion is its high incidence in women treated with aromatase inhibitors after breast cancer.[22] Oestrogen therapy alleviates arthralgia due to the menopause transition.

Vulvovaginal atrophy

The loss of oestrogen at menopause results in vulvovaginal atrophy. This affects approximately 70% of postmenopausal women,[23] causing vulvovaginal dryness, irritation, infection, sexual pain, arousal difficulties and decreased physical and emotional sexual satisfaction. Urogenital atrophy is also associated with recurrent urinary tract infections and urge and stress incontinence. Incontinence can severely impair quality of life. Studies consistently show the benefits of vaginal oestrogen for dyspareunia and urinary symptoms.

Bone density loss

The menopause is associated with loss of bone. This loss begins about two years before a woman has her final menstrual period, with the greatest loss occurring over the two years after the final period.[24] Bone loss tends to be less in women who are obese (body mass index of 30 kg/m^2 or higher). Oestrogen therapy reduces bone turnover, increases bone mineral density and decreases vertebral fracture rates by up to 40%.[25-27] It remains the treatment of choice for fracture prevention for many women.

Bone density measurement by dual-energy x-ray absorptiometry (DXA) is the standard method for diagnosing osteoporosis. There is uncertainty about screening women younger than 70 years for osteoporosis despite the fact that the rate of bone loss is highest in the perimenopausal period, rather than at older ages. Screening guidelines developed by the Royal Australian College of General Practitioners and endorsed by the NHMRC recommend screening women with risk factors that are not recognised by Medicare for reimbursement, such as low body weight, a family history of osteoporosis or being a smoker, as well as those recognised by Medicare.[28] There is a need for DXA screening guidelines and Medicare eligibility to be aligned. There is also a need for guidelines for the management of women diagnosed with osteoporosis without fracture, who are currently ineligible for nonhormonal fracture prevention therapy under the Australian Pharmaceutical Benefits Scheme.

Cardiovascular and diabetes risk

The loss of oestrogen at menopause also leads to central abdominal weight gain, which may occur with no change

in total body weight. This change from gynoid to android body shape, with an increase in truncal and subcutaneous abdominal fat mass, is associated with a higher likelihood of insulin resistance and a more adverse lipid profile (increased triglyceride and lower HDL cholesterol levels). In addition, levels of total cholesterol, LDL cholesterol and apolipoprotein B change across the menopause transition, increasing the risk of cardiovascular disease.

MANAGEMENT

When a woman presents to discuss menopause, this is an opportunity for a midlife health evaluation, as suggested in the box on page 40.

Diet and lifestyle

Individual trials and clinical guidelines indicate some women experiencing mild menopausal symptoms may gain a degree of benefit by modifying diet and lifestyle. Weight loss may reduce vasomotor symptoms for obese women.[29] There is no strong evidence to support exercise as a treatment for hot flushes.[30,31]

Hormone therapy

The most effective interventions for the treatment of menopausal symptoms are continuation of the combined oral contraceptive pill across the menopause transition or hormone replacement therapy. Although most publications advocate that hormone replacement therapy should be used at the lowest dose for the shortest possible time, this is not meaningful in clinical practice. In reality, if a woman elects to use this therapy then she should receive an effective dose, with the duration depending on the duration and severity of symptoms. Each woman should be assessed individually for her needs and risk factors. Treatment should be monitored every six months, with health checks and discussion about the need for ongoing treatment, dose and formulation.

Nonhormonal therapy

For women who choose not to take hormone therapy and for those with clear contraindications to hormone therapy, several nonhormonal therapies have been shown to lessen vasomotor symptoms. These include clonidine, gabapentin and selective serotonin reuptake inhibitors, with the latter having the additional benefit of improving mood in some women.

Complementary and alternative medicine

A review of published, quality trials of complementary and alternative medical (CAM) approaches to management of menopausal symptoms reported insufficient data to support the consistent effectiveness of these treatments.[32] Acupuncture has not been shown to have a meaningful effect on vasomotor symptoms.[32]

It is not uncommon for women to try a number of over-the-counter options or to see a CAM practitioner before discussing their menopausal symptoms with their doctor. An Australian study conducted in 2004 indicated that nearly 50% of complementary therapy users reported using conventional medicines on the same day, and 57% did not report their use of complementary therapy to their doctor.[33] This includes the use of treatments purchased via the internet, the extent of which cannot be estimated. Overall, these unapproved products are usually expensive, not subject to any quality control, often ineffective and, in some cases, potentially dangerous.

CONCLUSION

Menopause can cause a wide range of symptoms that potentially impair quality of life and can last for a few to many years. It is also associated with bone loss and increased cardiovascular and diabetes risk. Menopause is diagnosed clinically by a change in bleeding pattern in women with an intact uterus but requires hormonal measurement in those who have had a hysterectomy or endometrial ablation. The most effective treatment for menopausal symptoms is hormone therapy. Several nonhormonal therapies have been shown to lessen vasomotor symptoms in women who choose not to use or have clear contraindications to hormone therapy. MT

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References are included in the pdf version of this article available at www.medicinetoday.com.au.

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