



# Perimenopause

## A time of change

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### Key points

- The perimenopause begins with menstrual irregularity and continues until menopause, the complete cessation of menses.
- Symptoms reflect intermittent phases of deficiency and excess of oestrogen and can be difficult to differentiate from the effects of chronological ageing.
- Good preventive health care, close monitoring and early intervention in the perimenopause might help prevent progression to metabolic syndrome, cardiovascular disease, diabetes, obesity, osteoporosis and fractures.
- Quality of life is an important determinant in management of vasomotor symptoms and disturbances of sleep, mood and sexual functioning.
- The need for appropriate contraception should be remembered.

Fluctuating hormone levels during the perimenopause can lead to heavy and irregular menstrual bleeding along with menopausal symptoms. GPs can help women through this transition by providing information, relieving distressing symptoms and addressing modifiable health risks.

The perimenopause is a period of transition for women, involving significant changes, both physiological and psychosocial. It is important for GPs to look at the health risks and modifiable factors that can be addressed during the perimenopause to promote wellbeing and quality of life. Clinicians advising women in midlife need to distinguish between symptoms related to the changing hormonal milieu of the perimenopause (ovarian ageing) and those related to chronological ageing.

The definition of perimenopause is based on the bleeding pattern of a woman's menstrual cycle. The Stages of Reproductive Aging Workshop (STRAW) defines two perimenopause stages:<sup>1</sup>

- early perimenopause, which begins with increasing cycle irregularity and includes periods of amenorrhoea of up to three months
- late perimenopause, which includes periods

of amenorrhoea of more than three but less than 12 months; it ends with natural menopause, which is confirmed after 12 months of amenorrhoea (excluding surgical or physiological reasons for amenorrhoea).

There are no specific endocrine markers of these two stages of perimenopause.<sup>2</sup>

For women who have had a hysterectomy or endometrial ablation and those who have a progestin-releasing intrauterine device, the diagnosis of perimenopause can be challenging as there are no bleeding patterns on which to rely. The challenge is even greater for women who experience premature ovarian failure (menopause before the age of 40 years) or early menopause (before the age of 45 years). Similarly, women who continue taking the oral contraceptive pill into their 40s and early 50s may not know when they have reached perimenopause. Not uncommonly, however, women start to experience vasomotor symptoms despite using an

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### PROBLEMS ASSOCIATED WITH THE PERIMENOPAUSE

- Vasomotor symptoms – the most common presenting symptoms during perimenopause
- Sleep impairment – including sleep-onset and sleep-maintenance insomnia
- Depression – differing from major depression in features and treatment response
- Cognition problems – including memory problems
- Weight gain – increased fat mass and redistribution of fat to the abdomen
- Metabolic syndrome – associated with type 2 diabetes
- Cardiovascular risk
- Bone density loss
- Sexual dysfunction – vaginal dryness, dyspareunia, declining libido

ethinyloestradiol-containing systemic contraceptive. It appears that in some women synthetic oestrogen does not have the same effect as 17-beta-oestradiol, the oestrogen produced in the body, in preventing classic oestrogen deficiency symptoms.

### HORMONAL CHANGES IN PERIMENOPAUSE

The process of ovarian follicle loss occurs across a woman's lifespan and is greatest in utero.<sup>3,4</sup> The loss accelerates as a woman enters the perimenopause, accompanied by a change in the structural and functional quality of oocytes caused by ovarian ageing.<sup>5-7</sup>

The level of follicle-stimulating hormone (FSH) rises intermittently through the perimenopause, starting about six years before the last menses, with higher and more sustained levels in the late perimenopause.<sup>8</sup> FSH levels become stable about two years after the last menses, independent of age, ethnicity or smoking status.<sup>9</sup>

Oestradiol levels can be elevated in the follicular phase of the cycle in the early perimenopause and then decline towards the last menstrual period, becoming stable two years into the postmenopausal period.<sup>10</sup> However, the perimenopause is characterised by fluctuating oestrogen levels, which translate into fluctuating symptoms.

The level of inhibin B, derived from the granulosa cells of the ovarian follicles, declines as the follicular cohort shrinks. It is an early marker of the perimenopause and a measure of ovarian reserve.<sup>11</sup>

Anti-Müllerian hormone (AMH) is produced by the granulosa cells and levels decline over a woman's reproductive life. Low AMH levels suggest approaching ovarian failure, but the current lack of sensitivity of AMH measurement limits its clinical usefulness.<sup>9</sup>

Levels of the androgens testosterone and dihydrotestosterone as well as adrenal pre-androgen decline with age but are unaffected by natural menopause.

### DIAGNOSIS OF PERIMENOPAUSE

Hormone levels should not be used to determine whether a woman is perimenopausal, and hence should not be measured in most instances. The diagnosis of the perimenopause is based on changing menstrual cycle frequency and bleeding patterns, with or without symptoms. For women who have amenorrhoea due to hysterectomy, endometrial ablation or a progestin intrauterine device, the diagnosis is primarily based on symptoms. Hormone measurements are warranted if premature ovarian failure is suspected. Hormone measurements provide no useful information if a woman is using combined hormonal contraception (the oral contraceptive pill or the vaginal contraceptive ring).

### PROBLEMS OF PERIMENOPAUSE

Problems associated with the perimenopause are summarised in the box on this page.

### Vasomotor symptoms

Most women (80%) experience hot flushes or night sweats in midlife, with some racial and ethnic differences in prevalence.<sup>12</sup> Vasomotor symptoms are linked with lowered mood, sleep disturbance and poorer quality of life, and are more prominent in overweight women, smokers, women with low education and those with a history of depression. They classically commence in the perimenopause during menstruation and become more frequent as time passes. They can be intermittent over months or several years.

Vasomotor symptoms may also be associated with adverse health outcomes such as subclinical cardiovascular disease and lower bone density.<sup>13,14</sup> They are the most common menopause-related reason a woman seeks clinical advice during the perimenopause.

### Sleep impairment

Perimenopausal sleep disturbance exists as a specific disorder, distinct from other factors influencing sleep in women during the menopausal transition such as vasomotor symptoms, mood disturbance, sleep apnoea and age-related sleep changes. Both sleep-onset insomnia and sleep-maintenance insomnia are characteristically increased during perimenopause. In one study, poor sleep was not associated with decreasing oestrogen levels but rather a lower inhibin B level and a history of depression.<sup>15</sup>

Not only can poor sleep impair a woman's ability to function well through the day, but sleep deprivation has also been associated with metabolic syndrome.<sup>16</sup> Addressing sleep issues can greatly improve quality of life.

### Depression

There is a significant increase in vulnerability to depression during the perimenopause, and this is influenced by factors such as vasomotor symptoms and other perimenopausal somatic symptoms,

psychosocial stressors, general health issues, lifestyle and a history of depression.<sup>17</sup> This risk is likely to be affected by the reproductive hormone changes in the perimenopause.

Perimenopausal depression has characteristics different to those of major-depression, with symptoms of dysphoria associated with anger, irritability, hostility, tension and anxiety.<sup>18</sup> It is often described by women as similar to premenstrual dysphoria. Negative mood is of clinical significance because of the association between depression and adverse health outcomes, such as cardiovascular disease, diabetes, pain and impaired quality of life.

### **Cognition problems**

Self-reported memory problems are common in middle age. In one large study, perimenopausal women were 1.4 times more likely to report forgetfulness than premenopausal women, although many external reasons were perceived as the cause, such as work and family stress and multiple life roles.<sup>19</sup> Concomitant perimenopausal symptoms, poor sleep, hot flushes, anxiety and depression may also contribute to a decrement in cognitive performance, but this may stabilise in the postmenopausal period.

Management of modifiable risk factors for cardiovascular disease in the perimenopause may lessen the risk of progression to cognitive decline and dementia in later life.

### **Weight gain**

Obesity is a growing public health concern, and middle-aged women often report weight gain. Studies consistently show that the slow weight gain across the middle years is associated with age, not menopause.<sup>20</sup> However, the hormonal changes during the perimenopause are associated with an increase in fat mass and redistribution of fat to the abdomen.<sup>20</sup> This manifests as a change from a gynoid to an android pattern of fat distribution

and an increase in total body fat, which in turn increases the risk of developing metabolic syndrome and cardiovascular disease.

Obese perimenopausal women have altered hormonal dynamics, and heavier women tend to report more bothersome vasomotor symptoms early in the perimenopause.<sup>21,22</sup> Symptoms are more common and more severe with increasing body mass index. On the other hand, obesity protects to some extent against bone loss across the menopause transition.<sup>23</sup>

### **Metabolic syndrome**

Metabolic syndrome (impaired glucose metabolism, hypertension, dyslipidaemia and central abdominal obesity) is present in 20 to 30% of middle-aged women, increasing their risk of cardiovascular disease and diabetes.<sup>24</sup> The US Study of Women's Health across the Nation found an increase in incidence of metabolic syndrome from six years before to six years after the final menstrual period, independent of other risk factors such as weight gain and smoking.<sup>24</sup>

The main perimenopausal factor influencing progression to metabolic syndrome is the increase in intra-abdominal (visceral) fat that occurs when ovarian function ceases. Serum sex hormone binding globulin (SHBG), which transports sex steroids in the blood, is a strong independent marker of insulin resistance and type 2 diabetes risk and may play a role in the pathogenesis of type 2 diabetes and cardiovascular disease.<sup>25-27</sup> A low SHBG level strongly predicts increased visceral fat and metabolic syndrome.<sup>20</sup> Importantly, the relation between SHBG and insulin resistance in postmenopausal women is independent of both endogenous oestrogens and testosterone.<sup>28</sup>

The early perimenopause is a critical time to prevent abdominal weight gain.

### **Cardiovascular risk**

Cardiovascular disease (CVD) is the leading cause of death of women in Australia,

with premenopausal women having a lower risk than men until the time of the menopause.<sup>29</sup> It has long been debated whether this change in midlife is due to the loss of endogenous oestrogen (ovarian ageing) during the menopause transition or to chronological ageing, and whether women at high risk of CVD should use hormone replacement therapy to modify their risk, in addition to preventive lifestyle measures.

There are minimal lipid changes during the early perimenopause. However, from about a year before to a year after the final menstrual period there is an increase in total cholesterol, LDL cholesterol and apolipoprotein B levels and a decrease in HDL cholesterol and apolipoprotein A1 levels, consistent with a menopausal effect.<sup>30</sup>

In contrast, the changes in triglyceride, lipoprotein (a), insulin and factor VIIc levels and in systolic blood pressure are a consequence of ageing, not menopause.<sup>31</sup> Other markers of cardiovascular risk, such as highly sensitive C-reactive protein and fibrinogen levels and diastolic blood pressure, are not affected by menopause.<sup>32</sup>

### **Bone density loss**

Perimenopause is characterised by an increase in bone resorption and a reduction in bone mineral density (BMD).<sup>33</sup> These changes increase over the year before the final menstrual period and are greatest in the two years immediately afterwards. Assessment of bone turnover markers has been generally limited to research but this may change as more evidence emerges supporting their clinical use. Bone turnover markers should not be routinely measured in general practice.

Risk of fracture in the perimenopause increases with a low BMD, past history of fracture, non-use of hormone replacement therapy and smoking.<sup>34</sup> Structural bone geometry and risk of falls are also influencing factors.

### ASSESSMENT OF A WOMAN IN THE PERIMENOPAUSE

- Current and past health
- Family risk factors
- Smoking status
- Weight and waist circumference
- Blood pressure, lipid profile and cardiovascular risk
- History of deep vein thrombosis
- Detailed menstrual history to identify any vaginal bleeding requiring investigation (e.g. intermenstrual or postcoital bleeding, menorrhagia)
- Need for contraception
- Sexual dysfunction
- Depression
- Sleep issues
- Lifestyle (diet, physical activity, involvement in social activities)

### Sexual dysfunction

Aspects of sexual functioning include how important sex is to the individual, sexual desire, frequency of sexual activities, physical pleasure, emotional satisfaction with the partner, arousal and pain.

Early perimenopausal women in a large longitudinal study were 40% more likely to report pelvic pain with intercourse than premenopausal women, independent of vaginal dryness or age. In addition, libido declined across the menopause. Despite these changes, frequency of intercourse did not change significantly, such that women appeared to maintain their sexual functioning despite pain and lowered interest. Frequency of masturbation increased in the early perimenopause but declined from early to late perimenopause, along with sexual responsiveness.<sup>35</sup>

General and mental health factors are more significant determinants of sexual functioning than age or menopausal status.<sup>36</sup> Relationship status, social factors,

### PRINCIPLES OF MANAGEMENT OF THE PERIMENOPAUSE

- Ensure adequate contraception
- Control heavy or irregular menstrual cycles
- Relieve symptoms that affect quality of life, such as vasomotor symptoms, sleep impairment, mood disturbances and sexual dysfunction
- Assess and treat hypertension, metabolic syndrome and type 2 diabetes, if present
- Assess risk of cardiovascular disease
- Monitor lipid profile
- Encourage dietary and lifestyle modification to manage health risks
- Optimise bone health

the partner's health and a woman's previous sexual functioning are also important.

### Contraception

Fertility declines in a woman's mid-30s. Nevertheless, guidelines for providing adequate contraception recommend that women aged 50 years or younger should continue using contraception for at least two years following their last menstrual period, and women aged over 50 years should use contraception for one year following their last period. Age alone does not determine which method of contraception is appropriate.<sup>37</sup>

### MANAGEMENT OF PERIMENOPAUSAL PROBLEMS

Perimenopausal women may present with distressing symptoms that affect their quality of life. By the time of presentation, most have tried over-the-counter preparations for symptom control. Treatment is directed at:

- controlling irregular or heavy menstrual cycles

- ensuring adequate contraception
- relieving other distressing symptoms.

There is also an opportunity at this time for doctors to address other health behaviours and modifiable risks.

Assessment of a woman presenting with problems related to the perimenopause should cover the areas listed in the box on this page. Management may involve dietary and lifestyle modifications as well as pharmacological and non-pharmacological treatments. Principles of management of the perimenopause are summarised in the box on this page.

### Symptom relief and contraception

When selecting appropriate treatment for perimenopausal symptoms, the woman's need for contraception and her choice of contraceptive method should be considered, as well as the presence of any contraindications to hormone therapy and the woman's preferences regarding this therapy.

#### Contraception required

**Combined contraceptives.** For perimenopausal women needing contraception, the combined oral contraceptive pill provides contraception, regular, predictable and lighter withdrawal bleeds, and relief from vasomotor and other symptoms. It also preserves bone density, helps prevent ovarian and endometrial cancer, and treats the acne that can occur at this time. Each woman's risks must be assessed to determine the suitability of this approach.

A low-dose oral contraceptive pill (OCP) containing ethinyloestradiol (20 µg) and a progestin such as levonorgestrel (100 µg) or drospirenone (3 mg) can be used as first-line treatment. Vasomotor symptoms generally decline over two to three months. However, some women have persistent symptoms despite using a low-dose standard OCP and need to be switched to an OCP containing oestradiol valerate or oestradiol in micronised form. These OCPs deliver 17-beta-oestradiol, which is identical in

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molecular formula to the natural oestrogen produced in the body. Symptoms in the pill-free week can be managed by eliminating the inactive tablets or adding a low dose of supplemental oestrogen.

The controlled-release vaginal contraceptive ring provides contraception, regular predictable bleeds and symptomatic relief from vasomotor and other perimenopausal symptoms. It slowly releases ethinyloestradiol (15 µg per day) and etonogestrel (120 µg per day).

**Progestin-alone contraceptives.** Oral, injectable or intrauterine progestin-alone contraception may also be suitable. The levonorgestrel-releasing intrauterine device provides contraception and suppresses the endometrium, such that 80% of women are amenorrhoeic at one year. This is an excellent option to both manage menorrhagia and provide contraception. For

women with a levonorgestrel-releasing intrauterine device who experience oestrogen deficiency symptoms, the use of additional low-dose oestrogen therapy can be considered. However, as oestradiol levels fluctuate substantially during the perimenopause, the use of oestrogen therapy at this time may result in periods of supraphysiological oestradiol levels and hence breast pain, fluid retention and headaches.

**Barrier and other contraceptive methods.** Condoms, diaphragms, intrauterine devices and surgical sterilisation such as the laparoscopic clip or Fallopian tube inserts (which occlude the uterotubal junction) will have no effect on symptoms caused by oestrogen fluctuations.

#### *Contraception not required*

For women who do not require contraception and for those who use non-

hormonal methods, the newer OCPs containing micronised oestradiol or oestradiol valerate are still an excellent treatment option for perimenopausal symptoms. The use of OCPs is preferable in perimenopause to cyclical hormone replacement therapy that does not suppress ovulation because perimenopausal women still ovulate intermittently, and mostly unpredictably, and the use of oestrogen–progestin therapy without ovarian suppression commonly results in irregular bleeding. These OCPs provide cycle control and deliver oestradiol to ameliorate symptoms.

Younger women may elect to continue an oestradiol-containing OCP for several years because of its convenience. Women who commence menopause after the age of 50 years can usually be switched to a noncontraceptive hormone replacement regimen after

a couple of years, although there are no hard and fast rules.

### Nonhormonal symptom relief

Perimenopausal women with vasomotor symptoms who have contraindications to hormone therapy or choose not to use this therapy may obtain some relief from other treatments, such as selective serotonin or noradrenaline reuptake inhibitors, gabapentin or clonidine. However, the effects are less than for oestrogen.

### Female sexual dysfunction

Female sexual dysfunction across the perimenopause includes dyspareunia, diminished desire and arousal capacity, and difficulty in achieving orgasm. These symptoms can cause women profound distress and impact on their self-esteem, quality of life and relationships. Oestrogen therapy (topical or systemic) alleviates vaginal atrophy, and hence reduces vaginal dryness and dyspareunia, but does not improve other aspects of sexual functioning. Clinicians need to be mindful and to initiate discussion of sexual functioning in the perimenopausal years.<sup>38</sup>

Androgen therapy can be considered in women with a persistent low libido, as an adjunct to other hormonal and nonhormonal therapies or as the sole therapeutic agent.

### Prevention and monitoring

**Cardiovascular risk.** Assessment of cardiovascular risk, lipid monitoring and lifestyle modification should start before the menopause transition, with preventive interventions to minimise the future risk of progression to cardiovascular disease. Controversy over the use of hormone therapy to prevent cardiovascular disease continues, with later analysis of data from the Women's Health Initiative trials suggesting that initiation of hormone therapy close to the menopause reduces cardiovascular disease.<sup>39</sup>

**Hypertension, metabolic syndrome and type 2 diabetes.** If present, these conditions should be treated before the critical time period – the year immediately before and after the final menstrual period.<sup>31</sup>

This includes encouraging reduction in abdominal obesity and smoking cessation. **Osteoporosis.** There are no specific guidelines on the treatment and prevention of osteoporosis in perimenopausal women, but measures to optimise bone health are the same as for postmenopausal women. These measures include adequate dietary calcium and vitamin D intake, weight-bearing exercise, maintenance of a healthy weight, smoking cessation, avoidance of excessive alcohol and falls prevention.

### Complementary and alternative medicines

Despite the widespread use of complementary and alternative medicines (CAMs) in the community, few studies have shown evidence of their efficacy for vasomotor symptoms.<sup>40</sup> Published studies do not support the use of red clover, phytoestrogens, ginseng, evening primrose, dong quai or vitamin E for treatment of menopausal symptoms.<sup>41</sup>

Compounded hormonal preparations, promoted as 'bio-identical' hormone therapy, are also increasingly used. These preparations, formulated as lozenges, creams, gels and capsules, contain varying combinations of oestrogens, progesterone, pregnenolone, dehydroepiandrosterone (DHEA), testosterone and hydrocortisone. Pig or bovine thyroid extract is also co-prescribed at times for women with normal thyroid function and can have serious adverse health effects. These compounded hormone formulations are not approved by the TGA, and doses are not based on efficacy or safety data. There is no evidence that the doses of progesterone co-prescribed with compounded oestrogen therapy are adequate to prevent endometrial thickening and hyperplasia, potentially putting women at future risk of endometrial cancer. It is essential

that doctors who prescribe compounded hormones advise their patients that these preparations are not TGA approved and that there is no evidence they are safer than TGA-approved therapy.

### CONCLUSION

The perimenopause is a time when many women struggle with the changes in their lives. GPs are in a unique position to help women across this transition by opening discussion about the perimenopause, providing information and treating distressing symptoms. GPs can also take this opportunity to address a range of modifiable health issues and improve quality of life. **MT**

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References are included in the pdf version of this article available at [www.medicinetoday.com.au](http://www.medicinetoday.com.au).

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Dr Jane: None.

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