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Menopause-related symptoms and their treatment

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ABSTRACT

The menopause is a physiological event that occurs in all women who reach midlife. Symptoms shown to be associated with oestrogen deficiency after the menopause are hot flushes and night sweats, insomnia and vaginal dryness. However, many other symptoms and conditions (irregular menstrual bleeding, osteoporosis, arteriosclerosis, dyslipidaemia, depressed mood, irritability, headache, forgetfulness, dizziness, deterioration in postural balance, palpitations, dry eyes, dry mouth, reduced skin elasticity, restless legs, and muscle and joint pain) have also been implicated as associated with the menopause but are not necessarily correlated to oestrogen levels.

Oestrogens are effective in treating vasomotor symptoms, urogenital atrophy symptoms and irregular menstrual bleeding that occurs in the perimenopausal period. Conjugated oestrogens are given orally, and oestradiol may be given orally as tablets or transdermally as a patch or gel for a period of 3 weeks or longer. Perimenopausal women and women during the first 1 to 2 years after the menopause who have an intact uterus must be treated with a gestagen for at least 12 to 14 days every month in order to prevent endometrial hyperplasia and possible endometrial cancer. With this regimen the woman will have a withdrawal bleeding every month.

When the woman is 2 to 3 years postmenopausal then she can be recommended continuous administration of a fast combination of oestradiol and a gestagen that normally does not induce bleeding. Tibolone is an alternative substance (whose metabolites have both oestrogenic and gestagenic effects) that can also be used for the same indications as oestrogen preparations, the difference being that no additional gestagen is required.



KEYWORDS

Climacteric, gestagens, hormone replacement therapy (HRT), hot flushes, menopause, oestrogens, progestogens, urogenital symptoms, vasomotor symptoms

INTRODUCTION

The phenomenon of the menopause was known to the ancient Greeks; Aristotle (384–322 BC) described the cessation of menstruation at the age of 40. In the nineteenth century, the menopause was believed to be directly responsible for madness and even in more modern times it has still been believed to cause certain psychiatric illnesses.¹ The word ‘menopause’ is derived from *men* and *pausis* and is a direct description of the physiological event in women where menstruation ceases to occur. The word ‘climacteric’ is a Greek derivation of the ‘ladder’ or ‘steps of a ladder’. Over the years, the view of middle-aged women has varied from the extremes of either climbing up or down that ladder.⁵⁸ Symptoms associated with the menopause have also been known for a long time but it was not until the 1930s that climacteric symptoms could be effectively treated with oestrogens isolated from the urine of pregnant women.⁵ However, treatment was not very widespread until after the publication of Robert A Wilson’s best-selling book *Feminine Forever*,⁶⁰ after which treatment became more popular among physicians and women.

Symptoms that have been shown to be associated with oestrogen deficiency after the menopause are hot flushes and night sweats, insomnia and vaginal dryness.^{6,11,27,43} Many other symptoms and conditions (irregular menstrual bleeding, osteoporosis, arteriosclerosis, dyslipidaemia, depressed mood, irritability, headache, forgetfulness, dizziness, deterioration in postural balance, palpitations, dry eyes, dry mouth, reduced skin elasticity, restless legs, and muscle and joint pain) have also been implicated as associated with the menopause^{4,24,43} but are not necessarily correlated to oestrogen levels.^{45,51} An overriding issue regarding the biology and symptomatology of the menopause is its relationship to the underlying ageing process.

VASOMOTOR SYMPTOMS

Hot flushes are defined as transient, recurrent periods of heat sensation and redness, often concomitant with sweats. An increase in peripheral vasodilatation, skin temperature and skin moisture has been demonstrated during such episodes by the registration of skin conductance, thermograms or plethysmography in the affected areas of the face, neck, head or breast.⁵⁴ The duration is often 2 to 3 minutes but with a range from a few seconds up to one hour^{55,59} and there is a wide variety in frequency. Vasomotor symptoms are probably caused by changes in the temperature centre in the hypothalamus via different neurotransmitter systems as a result of fluctuations in oestrogen levels. The effect may also be mediated by β -endorphins, since low oestrogen levels after the menopause result in a more

labile gonadotrophin-releasing hormone (GnRH) secretion which may induce a sudden resetting of the thermoregulatory centre.⁵⁶ No direct correlation has been found between the severity of vasomotor symptoms and serum levels of sex steroids.^{45,51}

Vasomotor symptoms have been reported as occurring among women from different countries and societies but with varying prevalence. For example Mayan women³⁵ experience no hot flushes whereas in most western countries there is general agreement from both cross-sectional and longitudinal studies that 50–75% of postmenopausal women report hot flushes and night sweats of varying severity.^{14,16,33,34,47,52,57} This difference may be explained by genetic differences, different ways of identifying symptoms, different lifestyles and dietary habits.^{8,31,40,41,49} Vasomotor symptoms have been reported as most frequently experienced around the menopause but even 30–50% of women over 60 years of age experience symptoms.^{3,52,57} Women with a surgically induced menopause often have more severe symptoms compared to women with a natural menopause.^{11,50} However, it should also be noted that 10% of regularly menstruating women experience vasomotor symptoms³³ and 15–50% still report complaints 15 years or more after the menopause.^{3,30,43,52,57}

UROGENITAL SYMPTOMS

Vaginal atrophy and urogenital complaints such as vaginal discomfort, dysuria, dyspareunia and recurrent lower urinary tract infections are more common in women after the menopause.³⁸ Epidemiological studies^{26,38} have demonstrated that more than 50% of postmenopausal women suffer from at least one of these symptoms. Symptoms cause not only discomfort for the afflicted individual but may also negatively influence sexual health.^{1,30} Many women are so embarrassed by their 'hidden problems' that they are unable to discuss their dilemma with other women or their doctor.³⁸

Embryologically, the female genital tract and urinary systems develop in close proximity, both arising from the primitive urogenital sinus. Animal and human studies have shown that the urethra is oestrogen-sensitive, and oestrogen receptors have been identified in the human female urethra, urinary bladder, the vagina and the pelvic floor muscles.²⁵ Symptomatic and cytological changes have been demonstrated in the genitourinary tract during the menstrual cycle, in pregnancy and following the menopause.⁴⁴ In addition, factors influencing vaginal cytology, vaginal pH and the vaginal bacterial flora in elderly women have been identified.³⁷

Several features of the vaginal microenvironment change with increasing age, mostly in response to alterations in oestrogen and progesterone concentrations (Table 2.1).

The histology of the vagina changes extensively after the menopause, when the mucosa often becomes quite thin, and heavily infiltrated with neutrophils. Associated hormonal changes have also been shown to induce changes in the bacterial colonization of the vagina. After the menopause the vagina is colonized

**Table 2.1** Signs and symptoms of postmenopausal vaginal atrophy

Signs	Symptoms
Thinner epithelium	Dryness
Loss of rugae	Irritation
Reduced secretion	Burning
Reduced elasticity	Itching
Reduced width and length of vagina	Discharge
Altered bacterial flora	Dyspareunia

with a predominantly faecal flora in contrast to the dominance with lactobacilli encountered during the fertile period of life.^{37,44} The presence of lactobacilli in fertile women provides protection against vaginal and periurethral colonization by Gram-negative bacteria, which have been implicated in the pathogenesis of cystitis and urethritis. The diagnosis of vaginal atrophy can be simply made by taking a careful history complemented by a vaginal speculum inspection.

OTHER MENOPAUSE-RELATED SYMPTOMS

Many other symptoms and conditions (irregular menstrual bleeding, osteoporosis, arteriosclerosis, dyslipidaemia, depressed mood, irritability, headache, forgetfulness, dizziness, deterioration in postural balance, palpitations, dry eyes, dry mouth, reduced skin elasticity, restless legs, and muscle and joint pain) have also been implicated to be associated with the menopause⁴³ but are not necessarily correlated to oestrogen levels.^{45,51} Endometrial effects and bleeding patterns are dealt with in Chapter 22. The biology and consequences of osteoporosis (Ch. 8) as well as the prevention (Ch. 10) and treatment of osteoporosis (Ch. 9) are dealt with in this book. The influence of ageing and HRT on carbohydrate (Ch. 5) and lipid metabolism (Ch. 4) as well as cardiovascular diseases (Ch. 7) are also dealt with.

Sleep disturbance and insomnia during the climacteric have been recognized by some authors as directly caused by oestrogen deficiency.^{6,11,14,16,27,43} Some support for this opinion was provided in a randomized double-blind trial of the effect of transdermal oestrogen therapy on sleep. In this trial, short-term treatment with oestrogen replacement therapy improved objective sleep quality by alleviating the frequency of nocturnal movement arousals. However, other investigators have considered sleeping problems to be secondary to the occurrence of night sweats.^{18,33}

Several studies have indicated a possible correlation between depression and the menopause but most investigators have found no association between overt endogenous depression and oestrogen deprivation.^{12,15,19,29,32} However, milder mood changes and irritability are often related to severe climacteric symptoms.^{20,22,23,28} Women with previous premenstrual tension report more frequent severe vasomotor symptoms and depressed mood after the menopause.^{9,18,23,43}



THE TREATMENT OF MENOPAUSAL SYMPTOMS

Oestradiol and conjugated oestrogens are effective in treating the vasomotor symptoms, urogenital atrophy symptoms and irregular menstrual bleeding that occur in the perimenopausal period. Conjugated oestrogens are given orally and oestradiol may be given orally as tablets, transdermally as a patch or gel, or intranasally for a period of 3 weeks. Subdermal pellets or long-acting oestrogen injections have also been used. Perimenopausal women and women during the first 1 to 2 years after the menopause who have an intact uterus must be treated with a gestagen for at least 12 to 14 days every month in order to prevent endometrial hyperplasia and possible endometrial cancer. With this regimen the woman will have a withdrawal bleeding every month.

It is also possible to choose a preparation with a fast combination of oestrogen and gestagen using a sequential dosage regimen. Cyclical addition of the gestagen can with time be successively reduced to every other month or every third month in order to reduce the number of bleeding episodes. When the gestagen is not administered every month the possibility of endometrial hyperplasia must always be considered. If the woman desires a bleed-free regimen then the gestagen can be administered by means of an intrauterine system releasing levonorgestrel, which provides endometrial protection.

When the woman is 2 to 3 years postmenopausal she can be recommended continuous administration of a fast combination of oestradiol and a gestagen which normally does not induce bleeding. Tibolone is a substance whose metabolites have both oestrogen and gestagen effects, and which can also be used for the same indications as oestrogen preparations, the difference being that no additional gestagen is required.

There is a wealth of evidence to support the efficacy of hormone replacement therapy (HRT) in the treatment of climacteric symptoms such as vasomotor symptoms, urogenital symptoms and irregular bleeding in perimenopausal women. During the last two decades a debate has continued regarding the possible pros and cons of HRT. A large number of observational studies have shown that long-term use of oestrogens has prophylactic effects against coronary heart disease (CHD)^{13,53} and osteoporosis.¹⁰ However, recently randomized controlled studies such as the Women's Health Initiative trial⁴⁸ and the Heart and Estrogen/progestin Replacement Study (HERS)²¹ could not find evidence for primary or secondary preventive effects of HRT on CHD. An increased risk of breast cancer^{2,48} and venous thromboembolism^{7,48} among HRT users has also been reported.

Thus, in many countries, guidelines regarding treatment have been modified as a result of this new information. HRT is still recommended for the treatment of vasomotor symptoms but the duration of treatment should be reassessed on a yearly basis as long-term use (>5–10 years) appears to increase the risk of breast cancer. HRT should be continued as long as the benefits are judged to outweigh the risks. The risk of breast cancer appears to be greater when oestrogen is given in combination with gestagen as compared to oestrogen administration alone.



However, it should also be noted that the risk of breast cancer appears to return to baseline 5 years after the cessation of HRT.

Numerous studies have demonstrated a beneficial effect of oestrogen therapy in the management of vaginal atrophy; treatment with the oral, transdermal or vaginal application of oestrogens is also now well-established.^{17,36,39,42} Local vaginal application has been shown to be highly effective without inducing the systemic side-effects sometimes associated with oral or transdermal HRT. Oral or transdermal HRT given for the treatment of climacteric symptoms relieves vaginal atrophy symptoms for the majority of peri- and postmenopausal women.^{52,57} However, despite systemic therapy some women still experience vaginal symptoms. In these cases HRT can be complemented with local vaginal treatment with oestrogens, which can be given in the form of vaginal tablets or suppositories, vaginal cream or as a vaginal ring. Long-term compliance to HRT has also previously been reported to be a problem⁴⁶ and local treatment with oestrogens has been shown to be a simple, acceptable and effective alternative form of treatment for urogenital symptoms in postmenopausal women.

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