NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SCOPE

1 Guideline title

Menopause: diagnosis and management of menopause

1.1 Short title

Menopause

2 The remit

The Department of Health has asked NICE: ‘to produce a clinical guideline on the diagnosis and management of menopause’.

3 Clinical need for the guideline

3.1 Epidemiology

a) Menopause is a biological stage in a woman's life. It occurs when a woman stops menstruating, and it marks the end of her natural reproductive life. The changes associated with menopause occur when the ovaries begin to stop functioning. This includes the cessation of egg (oocyte) maturation and of oestrogen and progesterone secretion.

b) A woman has a finite number of oocytes at birth, which declines with each menstrual cycle. The menopause is characterised by the eventual depletion of a woman's oocyte store and cessation of menstruation. Menstrual cycle irregularity often occurs before periods stop completely.

c) Most tissues contain oestrogen receptors through which the hormone exerts its effects. The most immediate changes resulting from reduced oestrogen levels are evident in the regulation of the menstrual cycle. However, oestrogen depletion associated with the menopause has many other effects on the body – for example, causing vasomotor, musculoskeletal, urogenital and psychological symptoms. It has also been shown to have an impact on the function of other systems in later life, including bone and the cardiovascular system. Oestrogen depletion explains some of the differences in the incidence of osteoporosis between men and women.

d) Perimenopause, also called the menopausal transition, is the interval in which a woman has irregular cycles of ovulation and menstruation before the menopause.

e) A woman is defined as postmenopausal from 1 year after her last period. Within the UK population, the mean age of women who have a natural menopause is 51 years, although this can vary depending on different factors, including lifestyle.

f) Cross-cultural studies have shown that the age of menopause and its impact varies by ethnicity. For example, the US Study of Women's Health Across the Nation reported in 2009 that, on average, African–American women had more hot flushes than white women, and Asian women (Japanese or Chinese) had the fewest hot flushes of all ethnic groups surveyed. The same study reported that early menopause (between 40 and 45 years of age) affected 3.7% of African–American women, 2.9% of white women, 2.2% of Chinese women and 0.8% of Japanese women.

g) Premature ovarian insufficiency (also known as premature ovarian failure or premature menopause) is usually defined as menopause occurring before the age of 40 years. It can occur naturally or iatrogenically (that is, as a result of treatment). Premature ovarian

insufficiency and early perimenopause (menopause between the ages of 40 and 45 years) are associated with an increased risk of mortality, and with serious morbidity including cardiovascular disease, neurological disease, psychiatric disorders and osteoporosis. Lower socioeconomic status has been associated with premature ovarian insufficiency.

h) Many of the symptoms of the menopause are short lived and lessen or disappear over time. The most common include vasomotor symptoms (for example hot flushes and sweats), effects on mood (for example low mood) and urogenital symptoms (for example vaginal dryness). Of women responding to a postal survey carried out in Scotland in 2009 about symptoms experienced in the previous month, 47% reported hot flushes, 46% reported night sweats and 26% reported vaginal dryness.

i) Postmenopausal women are at increased risk of a number of long-term conditions, such as osteoporosis, cardiovascular disease and changes in the vagina and bladder. This is partly a result of oestrogen depletion.

j) There were more than 11 million women over the age of 45 years in the UK according to the Office of National Statistics 2011 census. This number has been steadily increasing and is forecast to continue to rise. The associated increase in the number of women going through the menopause is expected to result in more new referrals to secondary care – both of women needing short-term symptom control and of women who have associated long-term health issues.

3.2 Current practice

a) Two landmark studies, the Women's Health Initiative (2002) and the Million Women Study (2003), reported on the risks and benefits associated with the use of hormone replacement therapy (HRT).

The publication of these 2 studies was associated with a significant reduction in women's use of HRT in the UK.

b) A retrospective GP database study (2010) reported that 18% of women aged 45–64 years consulted their GP at least once in 1996 for menopause-related symptoms, but this fell to 10% of women in 2005. Furthermore, a cross-sectional study in 2012 found that more than 60% of women managed their menopausal symptoms without any contact with healthcare professionals, often through social support and obtaining advice from friends, family and the internet.

c) Variations in consultation patterns for menopausal symptoms depend on many factors, including cultural, ethnic, educational and psychosocial factors, as well as the impact of the symptoms on the women. However, it is currently thought that more than one-third of all women want more support for managing menopausal symptoms from their GP or practice nurse.

d) The information and support offered to women during and after the menopause is thought to be variable and, for some, inadequate. A UK-based survey published in 2007 indicated that most women would welcome more information about the menopause. To improve the information provided, and to facilitate women being able to make an informed choice, some professional groups have suggested that all women should be invited for a health and lifestyle consultation on their 50th birthday, which would include a discussion of menopausal symptoms and possible long-term sequelae of oestrogen depletion.

e) Treatments that have been used for menopause-related symptoms include lifestyle advice, HRT, herbal remedies, other complementary (alternative) therapies and antidepressants. In an internet survey (hosted at www.menopausematters.org.uk between 2005 and 2006), nearly three-quarters of women reported they did not know enough about HRT to make informed choices, 85% felt

they did not know enough to make informed choices about alternative therapies for menopause-related symptoms, and 95% said they would try alternative therapies before HRT in the belief that they are more ‘natural’ and because of concern over the health risks of HRT.

f) There is published evidence that physician speciality is significantly associated with HRT use. For example, in the USA women receiving care from gynaecologists are 2.6 times more likely to use HRT than that women receiving care from family physicians.

g) The use of HRT in the UK is strongly linked to socioeconomic status, with women of lower socioeconomic status being less likely to use HRT. Inequalities in referral rates have also been associated with geography and age.

h) The long-term benefits and risks of HRT are not fully agreed. The Women’s Health Initiative study found that HRT prevents osteoporotic fractures, but subsequent research suggested that there is an association between prolonged HRT use and increased rates of breast cancer and cardiovascular disease. However, the association between HRT and cardiovascular disease has since been disputed.

i) In summary, a large number of women in the UK experience menopausal symptoms, which in many cases can significantly affect their quality of life. Not all of these women seek medical treatment, and for those who do there is considerable variation in the help available.

4 The guideline

The guideline development process is described in detail on the NICE website (see section 6, ‘Further information’).

This scope defines what the guideline will (and will not) examine, and what the guideline developers will consider. The scope is based on the referral from the Department of Health.

The areas that will be addressed by the guideline are described in the following sections.

4.1 Population

4.1.1 Groups that will be covered

a) Menopausal women (covering the perimenopause and postmenopause).

b) Women with premature ovarian insufficiency (irrespective of cause).

4.1.2 Groups that will not be covered

a) Women who are pregnant.

b) Women who are breastfeeding.

c) Men.

d) Transgender women.

4.2 Healthcare setting

a) All settings in which NHS care is received or commissioned.

4.3 Clinical management

4.3.1 Key clinical issues that will be covered

a) Diagnosis and classification of the stages of menopause.

b) Optimal clinical management of menopause-related symptoms, including:

- treatments for symptomatic relief (specifically vasomotor, musculoskeletal and psychological symptoms, and altered sexual function), including:
  - hormonal pharmaceutical treatments:
    - oestrogen combined with progestogen (oral)
    - oestrogen combined with progestogen (transdermal)
    - oestrogen (oral)
    - oestrogen (transdermal)
    - oestrogen (depot)
    - progestogen alone
    - testosterone
    - tibolone
    - bio-identical hormones licensed for use in the UK
    - selective oestrogen-receptor modulators
  - non-hormonal pharmaceutical treatments:
    - selective serotonin reuptake inhibitors
    - serotonin–noradrenaline reuptake inhibitors
    - gabapentin
    - clonidine
  - non-pharmaceutical treatments:
    - phytoestrogens
    - herbal preparations (including black cohosh and red clover)
    - acupuncture
    - lifestyle advice
  - psychological therapies
    - cognitive behavioural therapy
- risks and benefits of treatments
- timing of treatment
- monitoring of treatment
- duration of treatment
- treatment withdrawal strategies

- information provision

Note that guideline recommendations will normally fall within licensed indications. Exceptionally, and only if clearly supported by evidence, use outside a licensed indication may be recommended. The guideline will assume that prescribers will use a drug's summary of product characteristics to inform decisions made with individual patients.

c) Contribution of HRT in preventing long-term sequelae of the menopause (especially osteoporosis and cardiovascular disease).

d) Diagnosis and management of premature ovarian insufficiency.

4.3.2 Clinical issues that will not be covered

a) Contribution of all other agents (excluding HRT) in preventing long-term sequelae of the menopause.

b) Systemic oestrogen-based hormonal treatment in women who have an increased risk of, or are undergoing treatment for, breast cancer.

c) Treatment of long-term sequelae of oestrogen depletion caused by menopause (especially osteoporosis and cardiovascular disease).

d) Premenopausal prevention of menopause-related symptoms (specifically vasomotor, musculoskeletal, urogenital and psychological symptoms and altered sexual function).

e) Investigation of the cause of premature ovarian insufficiency in women presenting with primary amenorrhea.

f) Induction of puberty in children and young people.

g) Cost-effectiveness analysis of methods of contraception during the menopause.

h) Tissue-selective oestrogen complexes[1]

4.4 Main outcomes

4.4.1 Short-term outcomes (up to 5 years of treatment)

a) Changes in menopausal symptom scores derived from a combination of menopausal symptoms (for example the Greene Climacteric Scale [GCS]).

b) Reduction in frequency or intensity of:

- vasomotor symptoms
- musculoskeletal symptoms
- psychological symptoms
- alterations in sexual function.

c) Treatment-related adverse effects.

d) Health-related quality of life.

4.4.2 Long-term outcomes

a) Mortality.

b) Coronary events (myocardial infarction or coronary death).

c) Stroke (ischaemic or haemorrhagic) or transient ischaemic attack.

d) Venous thromboembolism (pulmonary embolism or deep vein thrombosis).

e) Breast cancer.

[1] Tissue-selective oestrogen complexes are not licensed for any indication within the UK and therefore we are not able to consider this treatment within the guideline.

f) Osteoporotic fractures (hip and wrist fractures, clinically diagnosed vertebral fractures, total clinically diagnosed fractures).

g) Cognitive function and dementia (including Alzheimer's disease).

h) Type 2 diabetes

i) Health-related quality of life.

4.5 Review questions

Review questions guide a systematic review of the literature. They address only the key clinical issues covered in the scope, and usually relate to interventions, diagnosis, prognosis, service delivery or patient experience. Please note that these review questions are draft versions and will be finalised with the Guideline Development Group.

4.5.1 Diagnosis and classification of the stage of menopause

a) What is the accuracy of the following in the diagnosis of perimenopause and menopause compared with clinical diagnosis:

- menstrual cycle regularity
- symptoms (especially vasomotor symptoms)
- endocrine changes (specifically follicle-stimulating hormone, anti-Müllerian hormone, oestrogen or inhibin B) and total antral follicle count?

b) What is the effectiveness of classification systems such as STRAW +10 compared with non-structured classification systems in the diagnosis of menopause?

4.5.2 Optimal clinical management of short-term (up to 5 years) menopause-related symptoms

a) What information about the menopause do women find helpful?

b) What is the effectiveness (including risks and benefits) of different therapies compared with placebo and each other for the relief of individual menopause-related vasomotor symptoms, including:

- hormonal pharmaceutical treatments:
  - oestrogen combined with progestogen (oral)
  - oestrogen combined with progestogen (transdermal)
  - oestrogen (oral)
  - oestrogen (transdermal)
  - oestrogen (depot)
  - progestogen alone
  - testosterone
  - tibolone
  - bio-identical hormones licensed for use in the UK
  - selective oestrogen-receptor modulators
- non-hormonal pharmaceutical treatments:
  - selective serotonin reuptake inhibitors
  - serotonin–noradrenaline reuptake inhibitors
  - gabapentin
  - clonidine
- non-pharmaceutical treatments:
  - phytoestrogens
  - herbal preparations (including black cohosh and red clover)
  - acupuncture
  - lifestyle advice
- psychological therapies
  - cognitive behavioural therapy?

c) What is the effectiveness (including risks and benefits) of different therapies compared with placebo for the relief of individual menopause-related psychological symptoms, musculoskeletal symptoms and altered sexual function, including:

- hormonal pharmaceutical treatments:
  - oestrogen combined with progestogen (oral)
  - oestrogen combined with progestogen (transdermal)
  - oestrogen (oral)
  - oestrogen (transdermal)
  - oestrogen (depot)
  - progestogen alone
  - testosterone
  - tibolone
  - bio-identical hormones licensed for use in the UK
  - selective oestrogen-receptor modulators
- non-hormonal pharmaceutical treatments:
  - selective serotonin reuptake inhibitors
  - serotonin–noradrenaline reuptake inhibitors
  - gabapentin
  - clonidine
- non-pharmaceutical treatments:
  - phytoestrogens
  - herbal preparations (including black cohosh and red clover)
  - acupuncture
  - lifestyle advice
- psychological therapies
  - cognitive behavioural therapy?

d) At what intervals should clinical review be undertaken to assess the effectiveness and safety of treatments and to determine when women need to be referred to secondary care?

If HRT is found to be effective in 4.5.2b and 4.5.2c, the following question will be addressed:

e) In perimenopausal and postmenopausal women using HRT for symptom relief, what is the effectiveness of an abrupt HRT

discontinuation strategy compared with a tapered HRT discontinuation strategy?

4.5.3 Recognition and amelioration of the long-term sequelae of oestrogen depletion caused by menopause – specifically urogenital atrophy, osteoporosis and cardiovascular disease

a) What is the long-term effectiveness of local oestrogens for the treatment of urogenital atrophy?

b) What are the effects of HRT compared with placebo on the subsequent development of cardiovascular disease (including stroke) in women at different stages of the menopause?

c) What is the incidence of osteoporosis in:

- postmenopausal women who have used short-term HRT
- postmenopausal women who have used long-term HRT
- postmenopausal women who have not used HRT?

d) What are the effects of HRT administered for menopausal symptoms on the subsequent incidence of breast cancer, venous thromboembolism, early-onset dementia, sarcopenia and type 2 diabetes?

4.5.4 Diagnosis and management of premature ovarian insufficiency

a) What is the accuracy of the following in the diagnosis of premature ovarian insufficiency in women under 40 years with up to 12 months' amenorrhoea:

- menstrual cycle regularity
- symptoms (especially vasomotor symptoms)

- endocrine changes (specifically follicle-stimulating hormone, anti-Müllerian hormone, oestrogen or inhibin B) and total antral follicle count?

b) What is the effectiveness of HRT compared with combined oral contraceptives for the management of premature ovarian insufficiency?

4.6 Economic aspects

Developers will take into account both clinical and cost effectiveness when making recommendations involving a choice between alternative interventions. A review of the economic evidence will be conducted and analyses will be carried out as appropriate. The preferred unit of effectiveness is the quality-adjusted life year (QALY), and the costs considered will usually be only from an NHS and personal social services (PSS) perspective.

Further detail on the methods can be found in 'The guidelines manual' (see ‘Further information’).

4.7 Status

4.7.1 Scope

This is the final scope.

4.7.2 Timing

The development of the guideline recommendations will begin in August 2013.

5 Related NICE guidance

5.1 Published guidance

5.1.1 Related NICE guidance

- Familial breast cancer. NICE clinical guideline 164 (2013)
- Fertility. NICE clinical guideline 156 (2013).
- Osteoporosis. NICE clinical guideline 146 (2012).

- Epilepsy. NICE clinical guideline 137 (2012).
- Patient experience in adult NHS services. NICE clinical guideline 138 (2011).
- Alendronate, etidronate, risedronate, raloxifene, strontium ranelate and teriparatide for the secondary prevention of osteoporotic fragility fractures in postmenopausal women (amended). NICE technology appraisal 161 (2011).
- Alendronate, etidronate, risedronate, raloxifene and strontium ranelate for the primary prevention of osteoporotic fragility fractures in postmenopausal women (amended). NICE technology appraisal 160 (2011).
- Chronic heart failure. NICE clinical guideline 108 (2010).
- Denosumab for the prevention of osteoporotic fractures in postmenopausal women. NICE technology appraisal 204 (2010).
- Depression in adults. NICE clinical guideline 90 (2009).
- Advanced breast cancer. NICE clinical guideline 81 (2009).
- Early and locally advanced breast cancer. NICE clinical guideline 80 (2009).
- Heavy menstrual bleeding. NICE clinical guideline 44 (2007).
- Statins for the prevention of cardiovascular events. NICE technology appraisal 94 (2006).

5.2 Guidance under development

NICE is currently developing the following related guidance (details available from the NICE website):

- Urinary incontinence. NICE clinical guideline. Publication expected September 2013.
- Lipid modification (update). NICE clinical guideline. Publication expected July 2014.

6 Further information

Information on the guideline development process is provided in the following documents, available from the NICE website:

- How NICE clinical guidelines are developed: an overview for stakeholders the public and the NHS
- The guidelines manual.

Information on the progress of the guideline will also be available from the NICE website.