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EMAS position statement: The ten point guide to the integral management of menopausal health

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ABSTRACT

With increased longevity and more women becoming centenarians, management of the menopause and postreproductive health is of growing importance as it has the potential to help promote health over several decades. Women have individual needs and the approach needs to be personalised. The position statement provides a short integral guide for all those involved in menopausal health. It covers diagnosis, screening for diseases in later life, treatment and follow-up.

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Introduction

With increased longevity and more women reaching their 100th birthday, management of the menopause is of growing importance as it has the potential to help promote health over several decades. For most women the menopause is a natural and inevitable

process due to ovarian ageing which usually occurs in women in their late 40s or early 50s. However, it can be induced earlier by medical intervention such as bilateral oophorectomy or iatrogenic ablation of ovarian function by chemotherapy, radiotherapy or treatment with gonadotrophin-releasing hormone analogues. In the absence of surgery, induced premature ovarian failure may be permanent or temporary. EMAS is therefore producing a simple ten point guide to help physicians and allied health professionals from all specialities deal with menopausal and postreproductive health. It must be remembered that women have individual needs and the approach needs to be personalised.

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1. Key points in taking a medical history and examination

The most common conditions with which women present to healthcare professionals are concerns about bothersome vasomotor symptoms, sleep disturbance, mood swings, joint pains, osteoporosis or premature ovarian failure [1]. Assessment should include detailing symptoms and their impact on quality of life, menstrual history including age and type of menopause (natural or iatrogenic) and contraception [2]. Family or personal history should include that of breast, ovarian, endometrial and colon cancer; venous thromboembolism, migraine, and risk factors for osteoporosis, diabetes, hypertension, heart disease and stroke. The women's preference about treatment must be recorded. Physical examination should include recording of weight, height, waist-hip ratio and blood pressure.

2. Diagnosis of menopausal status

In women over 45 years irregular or absent menstruation especially in the presence of vasomotor symptoms is diagnostic of the menopause and in the vast majority of women no investigations are required [3]. In younger women with suspected premature ovarian failure or early menopause serial follicle-stimulating hormone (FSH) measurements should be undertaken. In menstruating women, measurement of FSH should be performed at the beginning of the follicular phase (days 2–5 of the cycle) to avoid ovulation-induced elevations of FSH. Measurement of thyroid stimulating hormone (TSH) and prolactin are also helpful in investigating menstrual irregularity. Pregnancy needs to be excluded. Estimates of the levels of luteinizing hormone, estradiol, progesterone and testosterone are of no value in the diagnosis of ovarian failure, but may provide information about other menstrual cycle disorders. Routine measurement of Anti-Mullerian Hormone (AMH) is not recommended to diagnose menopause in women over the age of 45, but may be helpful in women with suspected premature ovarian failure to assess ovarian reserve. However, while AMH has a relationship to age at menopause, the marked variability in levels needs further exploration and improved assay validity is required [4].

3. Screening for diseases in later life and forecasting menopause

Women should be encouraged to participate in national screening programmes for cervical, breast and colon cancer. Worldwide there are differences in the age at which screening programmes are started and stopped and in the screening interval. Individualised mammography according to risk may be preferred because of concerns regarding overdiagnosis with population screening programmes [5]. Patients at risk of osteoporosis are identified opportunistically using a case finding strategy [6]. FRAX can be used for people aged between 40 and 90 years, either with or without measuring bone mineral density. Assessment of cardiovascular risk and 10-year risk of a myocardial infarction could be also advisable, but again policies vary between countries [7]. Attempting to forecast the age of menopause with AMH measurements is controversial and should only be undertaken in at risk women (carriers of the fragile X gene (FMR1) permutation, family history of premature ovarian failure, those undergoing chemotherapy) in specialised centres [4,8].

In general pelvic assessment (examination and ultrasound) in asymptomatic women should be restricted to those at high risk of endometrial or ovarian cancer, but recommendations vary between countries [9].

4. Diet and lifestyle

There is increasing evidence that life-style factors, such as diet, physical activity, non-smoking and moderate alcohol consumption have a profound effect on health. The European EPIC study found that avoiding all inactivity would theoretically reduce all-cause mortality by 7.35% (95% CI: 5.88%, 8.83%) [10]. Women gain on average 10 kilos from 40 to 60 years. Whereas weight gain *per se* cannot be attributed to the menopause transition, the change in the hormonal milieu at menopause is associated with an increase in total body fat and an increase in abdominal fat [11]. Thus women should be encouraged to stop smoking, to have a balanced healthy diet rich in fibre, fruit and vegetables and to exercise regularly, aiming to prevent the midlife increase in body weight and to preserve their muscle mass [12,13]. With regard to hot flushes a Cochrane review concluded that 'evidence was insufficient to show whether exercise is an effective treatment for vasomotor menopausal symptoms' [14]. Some further studies show benefit [15] but a randomised controlled trial of 261 women in primary care found that that exercise is not an effective treatment for hot flushes or night sweats [16]. While women may consider complementary and alternative medicine to be a better natural option, the evidence of efficacy and safety is conflicting [17].

5. Management of hot flushes with and without estrogen

The most effective treatment for menopausal vasomotor symptoms is menopausal hormone therapy (MHT) with systemic estrogen. Benefits are more likely to outweigh risks for symptomatic women before the age of 60 years or within 10 years after menopause [18]. Estrogen alone is given to hysterectomized women. Progestogens are added in regimens for non-hysterectomized women to reduce the increased risk of endometrial hyperplasia and carcinoma, which occurs with unopposed estrogen. The two main routes of administration are oral and transdermal (patches and gels). While most progestogens are given orally, norethisterone and levonorgestrel are available in transdermal patches combined with estradiol; and levonorgestrel can be delivered directly to the uterus with an intrauterine device. The use of custom-compounded bioidentical hormone therapy is not recommended [18]. Approved by the US Food and Drug administration in 2013 and the European Union in 2014 a new development is the use of the selective estrogen modulator bazedoxifene instead of a progestogen combined with conjugated estrogen [19].

Tibolone is a synthetic steroid compound that is in itself inert, but whose metabolites have estrogenic, progestogenic and androgenic actions. It is classified as MHT and is used in postmenopausal women.

Symptom control is used to determine the minimum required dose for each woman and anecdotally those with premature ovarian failure (POF) need a higher dose of estrogen to control vasomotor symptoms than their older counterparts. Except for women with POF (see below) treatment for vasomotor symptoms treatment can be continued for up to 5 years and then stopped to see if they are still present. While most women will no longer have symptoms at that stage, one should be aware that some will experience hot flushes long-term even lifelong. There are no arbitrary limits regarding the duration of use of MHT. In the absence of contraindications it can be used for as long as the woman feels the benefits outweigh the risks for her and decisions must be made on an individual basis [20].

When balancing benefits and risks dose, type and route of administration need to be considered. For example risk of venous thromboembolism is less with transdermal compared to oral

estrogen administration. Unopposed estrogen does not increase the risk of breast cancer and use of progesterone or dydrogesterone rather than synthetic progestogens is associated with reduced risk of breast cancer and venous thrombosis [21].

Non-estrogen-based therapies are available for women who do not wish to take estrogen or have a contraindication (such as a personal history of breast cancer or venous thromboembolism) [22]. Paroxetine, fluoxetine, citalopram, venlafaxine, desvenlafaxine, clonidine and gabapentin have been found to be effective for hot flushes in several studies. However these are less effective than estrogen. Paroxetine and fluoxetine are potent cytochrome P450 2D6 (CYP2D6) inhibitors and decrease the metabolism of tamoxifen and may reduce its anticancer effect and thus should be avoided in tamoxifen users. Stellate ganglion block (SGB), achieved by injecting an anaesthetic such as bupivacaine under fluoroscopic guidance around the stellate ganglion, may help with vasomotor symptoms but the evidence is conflicting [23].

The use of androgen therapy is controversial. Although surgical menopause represents an androgen-depleted state, the prevalence of subsequent sexual dysfunction is unknown. However, women choosing (as opposed to just consenting to) bilateral oophorectomy with a simple hysterectomy required for benign reasons do not develop sexual dysfunction over the next one to three years [24]. Thus women should be carefully assessed before recommending androgens and therapy may be used alone, combined with estrogen and psychosexual counselling [24,25]. Reassuringly testosterone does not appear to increase the risk of breast cancer [26].

6. Genitourinary syndrome of menopause

The term *genitourinary syndrome of menopause* (GSM) is now replacing *vulvovaginal atrophy* as it is thought to be a medically more accurate term [27]. GSM is defined as a collection of symptoms and signs associated with a decrease in estrogen and other sex steroids involving changes to the labia majora/minora, clitoris, vestibule/introitus, vagina, urethra and bladder. The syndrome may include but is not limited to genital symptoms of dryness, burning, and irritation; sexual symptoms of lack of lubrication, discomfort or pain, and impaired function; and urinary symptoms of urgency, dysuria and recurrent urinary tract infections.

Topical estrogens, lubricants and moisturisers or ospemifene can be used. Topical estrogen preparations include estradiol-containing tablets and rings; estriol pessaries, creams, gels and ovules; promestriene and conjugated estrogens [28]. They can be used alone or combined with systemic MHT. There is no need to add a progestogen for endometrial protection when topical estrogens are used in the recommended doses. With regard to duration of use, recommendations vary between preparations, but vaginal atrophy is a chronic condition and will recur on cessation of treatment. Data in women with breast cancer with low dose topical estrogen are scant. However, in view of these concerns, nonhormonal lubricants and moisturisers should be considered first line [29].

Approved in both the US and Europe the orally administered selective estrogen receptor modulator ospemifene is a new treatment option for women. Evidence of efficacy of ospemifene is based on randomised controlled trials and long term safety data are available [30]. The approved indication in Europe is for '*treatment of moderate to severe symptomatic vulvar and vaginal atrophy (VVA) in post-menopausal women who are not candidates for local vaginal oestrogen therapy*'. The most common side effects are hot flushes [31].

Finally women with urinary symptoms or vulval changes should be encouraged to undergo diagnosis and treatment [32,33].

7. Conserving the skeleton and musculoskeletal health

Both randomised (WHI) and observational studies show that MHT reduce the risk of osteoporotic fracture but estrogen-deficient bone loss will resume on stopping therapy. Estrogen-based therapy is the treatment of choice for women under the age of 60 or within 10 years of menopause [18].

Non-estrogen based treatments for osteoporosis includes bisphosphonates, denosumab, selective estrogen receptor modulators (SERMs), parathyroid hormone (PTH) and strontium ranelate [34–36]. However the data on efficacy are mainly restricted to women aged 60 or over. Bisphosphonates (such as alendronate, risedronate, ibandronate, and zoledronic acid) inhibit bone resorption by inducing apoptosis of osteoclasts, thus preventing age related bone loss and deterioration of bone microarchitecture. They are the most widely prescribed drugs, mainly due to their low cost and the generally favourable safety profile. Denosumab is a human monoclonal antibody to the receptor activator of nuclear factor-kappaB ligand (RANKL), a bone resorbing cytokine. It is administered as a subcutaneous injection every six months. All anti-resorptive agents are associated with an increased risk of osteonecrosis of the jaw and atypical femoral fracture. But both conditions are rare. The two SERMs approved for the treatment of postmenopausal osteoporosis are raloxifene and bazedoxifene. Both reduce the risk of vertebral but not hip fracture and increase the risk of venous thromboembolism and hot flushes. They are both associated with a decreased risk of breast cancer in postmenopausal women with osteoporosis.

Some therapies have restrictions on their use. Thus the use of strontium ranelate is restricted to people who cannot be treated with other medicines approved for osteoporosis because of concerns about increased risk of cardiovascular disease [37]. The use of PTH in postmenopausal women at high risk of fractures (to reduce the risk of vertebral fractures) is limited to 2 years because of concerns about the increased risk of osteosarcoma found in rat, but not human, studies [38].

Future treatments for osteoporosis include cathepsin K inhibitors which appear to have mixed antiresorptive and anabolic actions as they inhibit one of the major osteoclast digestive enzymes without suppressing bone formation, thereby leading to anabolic effects on bone [39]. New biologic agents in clinical trials include anti-sclerostin and anti-dickkopf antibodies that stimulate the Wnt/ β -catenin pathway in osteoblasts, leading to new bone formation [40].

It is must not be forgotten that integral to osteoporotic fracture prevention are strategies to reduce falls and conserve muscle mass and ensuring that women are calcium and vitamin D replete [15,35,41,42].

8. Premature ovarian failure

In women with POF, systemic estrogen-based MHT is recommended at least until the average age of the natural menopause, unless it is contraindicated [18,43]. Untreated it increases the risk of osteoporosis, cardiovascular disease, dementia, cognitive decline and Parkinsonism [44]. In women under the age of 50 MHT use is not associated with an increased risk of breast cancer compared to that found in normally menstruating women. Ovulation may occur intermittently after diagnosis of POF, possibly resulting in menstrual bleeding and pregnancy and thus fertility and contraception need to be discussed. There are no data regarding efficacy, long term use and safety of non-estrogen based treatments for osteoporosis. Furthermore there are no data on the long term effects on the skeleton of exposed offspring should pregnancy occur.

9. Contraception in the perimenopause

While fertility declines with age, sterility cannot be assumed. Spontaneous pregnancies have been reported in women in their late 50s. Thus contraception in the perimenopause is an important issue [45]. There are no contraceptives that are contraindicated based on age alone [46]. Contraception for women in this age group has specific risks and benefits; both should be balanced to choose between the different options available. The general advice is that contraception should be used for 2 years after the last menstrual period in women aged under 50 and 1 year in those over 50. The final menstrual period may however, be difficult to identify in women taking sequential HT which induces a cyclical withdrawal bleed or using intrauterine levonorgestrel to provide the progestogen component of the regimen which induces amenorrhoea. Elevated levels of follicle-stimulating hormone (FSH) do not reliably indicate infertility in HT users even in the hormone-free interval of sequential therapy. The method used should be acceptable for that individual taking into account their medical eligibility criteria. All estrogen-based contraceptives (pills, patches, vaginal rings) can be used in women without cardiovascular or thrombotic risk factors. The so-called second generation combined oral contraceptives (COC) should be used preferentially and the 3rd and 4th generation COC should be reserved for special indications [47].

Systemic MHT is not contraceptive. Barrier methods (condoms, caps), spermicides and copper bearing intrauterine devices can be used by MHT users. Postmenopausal women should continue to use condoms to reduce the risk of sexually transmitted diseases. Non-oil based lubricants are not recommended with latex condoms as they can cause rupture. A progestogen-only pill can be used in HT users to provide effective contraception but the regimen must include progestogen in addition to estrogen to ensure endometrial protection. Intrauterine levonorgestrel (LNG-IUS) provides effective contraception and the progestogen component of MHT as well as being an effective treatment for heavy menstrual bleeding.

10. Follow-up and assessment

Follow-up should be individualised and depends on whether the woman is taking any medication. For those who simply wanted advice no routine follow-up is required. However, women should be made aware that they can come back for further discussion if symptoms or concerns about chronic conditions, such as osteoporosis, change. After a review at around 3 months to resolve any initial issues, women taking MHT should have at least an annual consultation to assess efficacy, dose, type, route of administration and need for continued treatment. Changes in the balance of benefits and risks need to be ascertained. Women with POF may need more frequent visits because of the adverse health consequences of untreated menopause and should be seen until the average age of the natural menopause [48]. There is currently no indication for increased mammographic or cervical smear screening in MHT users. Women taking non-estrogen based treatments for osteoporosis should be reviewed to ascertain continued use of therapy and monitoring response with bone mineral density assessments or biochemical markers to maximise benefits and minimise risks [49,50].

Contributors

Prof. Margaret Rees prepared the initial draft, which was circulated to all authors for comment and approval; production was coordinated by Prof. Margaret Rees.

Competing interests

In the last 2 years, Martin Birkhaeuser has been a member of advisory boards and a speaker at sponsored symposia of the following pharmaceutical companies: Abbott, AMGEN, Bayer Schering, Bionorica, Daiichi Sankyo, HEXAL, MSD, Novartis, Pfizer, Vifor-Galenica. S. Palacios has been a symposium speaker or advisory board member for Servier, Pfizer, GSK, Abbott, Ferrer, Bioiberica, Shionogi and Amgen and has received research grants and/or consulting fees from Pfizer, Servier, Amgen, MSD, Preglem, Leon Farma, and Gynea. P. Llana has been a speaker at sponsored symposia of the following pharmaceutical companies: AMGEN, Pfizer and Shionogi.

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