



EMAS position statement: Managing obese postmenopausal women

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ABSTRACT

Introduction: Obesity is a public health problem, with overweight individuals representing approximately 20% of the adult world population. Postmenopausal status is associated with higher prevalence of obesity, as 44% of postmenopausal women are overweight, among whom 23% are obese. Obesity often co-exists with other diseases, the most important being diabetes mellitus, dyslipidemia and hypertension. Furthermore, obesity increases the risk of gynecologic cancer, cardiovascular disease, venous thromboembolism, osteoarthritis and chronic back pain.

Aim: To formulate a position statement on the management of the menopause in obese women.

Materials and methods: Literature review and consensus of expert opinion.

Results and conclusions: Obese women seeking hormone therapy should be evaluated for their individual baseline risk of developing breast cancer, cardiovascular disease and venous thromboembolism. These risks should be weighed against expected benefit from symptom relief, improved quality of life and osteoporosis prevention. The lowest effective estrogen dose should be used (CEE 0.300–0.400 mg or estradiol 0.5–1 mg orally daily or 25–50 µg estradiol transdermally). With regard to progestogens, although no RCT data exist, there are observational studies showing that micronized progesterone or dydrogesterone may have a better risk profile with respect to breast cancer risk. There are no RCT data comparing various progestogens with regard to VTE risk. There are observational data, however, suggesting that micronized progesterone or pregnane derivatives may be associated with a lower VTE risk in postmenopausal women taking HT compared to nonpregnane derivatives. There is a rationale in suggesting the use of transdermal HT in obese women, since this route of administration has been associated with a lesser risk of venous thromboembolism than oral therapy.

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1. Introduction

Obesity is a very common public health problem, especially in the western hemisphere. According to the World Health Organization (WHO), there are 1 billion overweight adults worldwide, among whom 300 million are obese [1]. The prevalence of obesity in postmenopausal women is proportionally higher, compared to premenopausal women [2]. Contributing factors are increasing age, which is associated with lower basal metabolic rate, lower energy expenditure due to more sedentary life-style and increased caloric intake. The menopausal transition per se is also associated with weight gain, predominantly in the trunk region, leading to central

obesity [3]. Obese postmenopausal women differ from the general postmenopausal population mainly in relation to the following issues:

- (1) Hot flushes and menopausal symptoms in general are more frequent in obese women compared to women with normal BMI. In the SWAN study, the odds ratio for hot flushes was 1.27 for each standard deviation increase in percental body fat [4]. Women who gain weight during the menopausal transition are more prone to have menopausal symptoms [5].
- (2) Obese postmenopausal women are at increased risk of developing coronary heart disease (CHD). According to the Nurses' Health Study, 5 kg/m² increase in BMI is associated with an 30% increase in the incidence of CHD in women, independently of other CHD risk factors, such as age, smoking, physical activity, alcohol intake or family history of CHD [6,7].
- (3) Stroke risk increases linearly with increasing BMI independently of sex and race [8]. Data from the Nurses' Health Study

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show that women with BMI >32 kg/m² have a relative risk of 2.37 of developing ischemic stroke. Furthermore, women who gain 10–20 kg during their adult life have a 69% increase in the risk of ischemic stroke [9].

- (4) Obesity is associated with increased risk of venous thromboembolism (VTE). VTE is rare in premenopausal and young postmenopausal women and its incidence increases with age, BMI and the presence of prothrombotic mutations (Factor V-Leiden and Prothrombin G20210A). Obese women in the placebo arm of the Women's Health Initiative (WHI) trial had 2.9 increased risk of developing VTE compared to women with normal BMI [10].
- (5) Obese postmenopausal women are at increased risk of developing breast cancer. Obesity is associated with a relative risk of breast cancer ranging between 1.26 and 2.52. According to a meta-analysis on 2.5 million women, a 5 kg/m² increase in BMI is associated with 12% increase in the incidence of breast cancer [11]. Possible explanations are the higher endogenous estrogens produced by the aromatization of precursor adrenal and ovarian androgens in adipose tissue and mitogenic IGF-1 activity associated with insulin resistance. Apart from absolute body weight, the weight gained after 30th–40th year of age and especially perimenopausally appears to constitute an extra risk of breast cancer [11,12].

The aim of this position statement is to provide evidence-based advice on the management of obese postmenopausal women.

2. Hormone therapy (HT)

HT is the most effective treatment of menopausal symptoms and urogenital atrophy. HT in general is safe in young recently menopausal women, since the expected benefits usually outweigh possible risks. With regard to CHD, there is increasing evidence that if HT is given in the first decade after the menopause, it may confer cardioprotection, while in older women with already diseased vessels, the prothrombotic and proinflammatory effects of estrogens may prevail leading to increased CHD events [13]. Regarding stroke, there is a small but significant risk associated with oral HT at all ages, the absolute risk, however, is small in young women [14,15]. VTE risk in oral HT users is 2–3 times higher compared to non-users [16]. Breast cancer risk is apparent after 3–5 years of use, increases with duration of use and is higher with combined estrogen/progestogen regimens [17]. The risks can be reduced by carefully evaluating every woman and selecting patients with low baseline risk. Furthermore, the HT regimen should be individualized, based on the case – specific risk, with respect to the type of estrogen and progestogen, the dose (younger women usually require a higher dose for symptom relief), the route of administration and the duration of use. Obese symptomatic postmenopausal women should not be prevented from taking HT, since it is an effective treatment. Special consideration should be given to baseline assessment, selection of HRT regimen and follow-up.

2.1. Baseline assessment

If a health professional is evaluating whether or not an obese woman should take HT, they should assess the indications (symptom control, osteoporosis prevention) and risks (breast cancer, cardiovascular disease, VTE).

Breast cancer risk factors include inherited gene mutations BRCA1/2, family history of breast cancer, personal history of benign breast disease, daily alcohol intake, past history of HT use, advanced age at 1st delivery, nulliparity, young age at menarche, late menopause and increased mammographic density. Mammog-

raphy before starting HT should be undertaken in accordance with national guidelines. It should be noted that, although obese postmenopausal women have an increased baseline breast cancer risk, HT may not further increase it. The increase in risk is probably more apparent in lean postmenopausal women taking long term HT [18].

Beyond obesity, cardiovascular disease (CVD) traditional risk factors include age, smoking, arterial hypertension, diabetes mellitus and dyslipidemia (high LDL-cholesterol, high triglycerides, low HDL-cholesterol). Emerging risk factors for CHD are C-reactive protein, lipoprotein (a), homocysteine, leukocyte count, fasting blood glucose, coronary artery calcium score, carotid intima-media thickness and periodontal disease [19]. Additional risk factors for a stroke are atrial fibrillation and left ventricular hypertrophy. It should be noted that hypertension, elevated triglycerides and low HDL are stronger risk factors for cardiovascular events in women compared with men [1,20]. Obese women are more prone to have one or more coexisting risk factors [21]. Thus HT should be avoided in women with a significantly increased baseline risk of CVD. For example, a 56-year old obese diabetic smoker with 150 mm Hg systolic pressure taking antihypertensive medication has a 10-year Framingham risk score [22] for any CVD event >30% and should be advised against HRT. On the other hand, a 56-year old obese non-smoker, non-diabetic woman with 110 mm Hg systolic blood pressure taking antihypertensive medication has 10-year risk for any CVD event ≤5% and is a candidate for HRT [22].

A family history of VTE or a personal history of VTE after combined oral contraceptive use or postpartum are significant risk factors for future events. General screening for thrombophilic mutations is generally not recommended. Given, however, the increased baseline VTE risk in obese women, it might be useful to screen for V-Leiden and prothrombin G20210A mutations in this specific population though this is debated. Carriers of these mutations, especially of Factor V-Leiden, should be advised against taking oral HT, since the hormone-associated risk of VTE is 6.7-fold increased in these women [10,16].

2.2. Selection of HT regimen

2.2.1. Estrogen

There are neither head-to-head trials, nor observational data comparing estradiol with CEE, so no recommendations can be made with regard to one compound over the other. The lowest effective dose should be used, starting with 0.5–1 mg oral estradiol or 0.300–0.400 mg oral conjugated equine estrogens (CEE) or 25–50 µg transdermal estradiol daily. There is evidence from observational data that lower estrogen dose may have a lesser impact on mammographic density [23,24], stroke [25] and VTE [26].

2.2.2. Progestogen

There are no RCT data comparing various progestogens with regard to VTE and breast cancer risk. There are observational data, however, suggesting that micronized progesterone or pregnane derivatives may be associated with a lower VTE risk in postmenopausal women taking HT compared to nonpregnane derivatives [27,28]. Since obese patients have an increased baseline risk of breast cancer and the observational French E3N cohort indicates that the addition of micronized progesterone or dydrogesterone to estrogen may be associated with a smaller increase in breast cancer risk compared to other synthetic progestogens, there is a rationale to favor micronized progesterone or dydrogesterone [29,30].

2.2.3. Route of administration

The route of HT administration does not appear to have an effect on HT-associated breast cancer risk. Furthermore, no RCT data are

available on the effect of transdermal estrogen on VTE risk. There is accumulating evidence, however, that transdermal estrogen may not exhibit the increased risk of VTE associated with oral estrogen. The ESTHER study reported a non-significant relative risk of 0.9 for transdermal estrogens, compared to a significant risk of 4.2 associated with oral estrogens [27]. Similarly a recent meta-analysis of observational studies has reported no increased VTE risk for transdermal estrogens (RR 1.2), in contrast to a pooled relative risk of 2.5 of women taking oral estrogen [16]. Women in the E3N cohort taking transdermal estrogens had no increased thrombotic risk (OR 1.1) in contrast to oral estrogen users (OR 1.7) [28].

Overweight and obese women taking oral HT in the WHI trial had an odds ratio of 3.8 and 5.6 for venous thrombosis respectively, compared to non-users with normal BMI [10]. Concerning the estrogen – only arm of the WHI study, the odds ratio for venous thrombosis was 2.7 and 4.3 for overweight and obese women respectively [31]. These figures were higher in the ESTHER study: the odds ratio for overweight and obese women taking oral HT was 10.2 and 20.6 respectively, compared to women with normal BMI not using HRT. However, obese women in the ESTHER study taking transdermal HT had no increased risk for thrombosis compared to obese non-users [32]. Although no RCT data exist, transdermal HRT should be the first choice for obese postmenopausal women.

2.2.4. Duration of treatment

Duration of treatment should be assessed on an individual basis, weighing up osteoporosis risk, persistence of menopausal symptoms and decline of quality of life after an attempt to taper or stop HT against breast cancer, VTE and stroke risk.

2.2.5. Tibolone

Tibolone is effective in treating menopausal symptoms. It conserves bone mass and reduces the risk of vertebral and non-vertebral fractures particularly in patients who had already had a vertebral fracture. It also may reduce the risk of invasive breast cancer and colon cancer, but it does not significantly reduce the risk of hip fracture, and it increases the risk of stroke [33]. There are no specific data regarding tibolone and obesity.

3. Non hormone therapy-based treatments

Non-estrogen based treatments are used to treat hot flushes and symptoms of urogenital atrophy. These include clonidine, selective serotonin reuptake inhibitors (SSRIs) and serotonin and noradrenaline reuptake inhibitors (SNRIs), gabapentin and vaginal lubricants and moisturisers [34]. There are no specific trials concerning the impact of obesity regarding the effectiveness or side effects of these drugs.

4. Conclusion

In conclusion, obesity poses a serious health burden, since it is associated with various co-morbidities, such as arterial hypertension, dyslipidemia, diabetes mellitus; and furthermore, with increased risks of breast cancer, CVD and VTE. Obese postmenopausal women requiring HT should be thoroughly evaluated at baseline and the severity of symptoms and risk of fracture should be weighed against individual risks of breast cancer, CVD and VTE. Although, there is a lack of specific data in obese patients, once the decision is made to commence HT, there is a rationale to use the lowest effective dose (estradiol 0.5–1 mg orally or 25–50 µg transdermally), and may be to prefer using the transdermal route.

5. Summary recommendations

- Obesity is a public health problem, with overweight individuals representing approximately 20% of the adult world population.
- Postmenopausal status is associated with higher prevalence of obesity, as 44% of postmenopausal women are overweight, among whom 23% are obese.
- Obesity increases the risk of diabetes, cardiovascular disease, breast and gynecological cancer, venous thromboembolism, osteoarthritis and chronic back pain.
- Obese women seeking hormone therapy should be evaluated for their individual baseline risk of developing breast cancer, cardiovascular disease and venous thromboembolism.
- The lowest effective estrogen dose should be used (CEE 0.300–0.400 mg or estradiol 0.5–1 mg orally daily or 25–50 µg estradiol transdermally).
- Transdermal HT may be preferred since data support that this route of administration has a lesser risk of venous thromboembolism than oral therapy.

Competing interests

None declared.

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Provenance

EMAS position statement.

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