Consensus of the Belgian Menopause Society regarding therapy and strategies after the menopause

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Background

- The use of menopause hormone therapy has dramatically decreased in all countries since the initial findings of the Women's Health Initiative (WHI) were published in 2002.
- Physicians' advices and women's decisions regarding such therapy have been surrounded by anxiety and confusion for the last decade.
- Moreover a generation of physicians have not been trained about menopause management.

Aim

- To develop a consensus about the use of Menopause Hormone Therapy (MHT)

Methodology

- These experts came together repeatedly and proposed the following consensus based on recent and updated publications.
- They essentially considered meta-analyses, randomised trials and large epidemiological observational studies. This is the last update of previous consensus statements.
- The experts hope that this document will facilitate practical menopausal management. The proposed consensus represent the shared view of these experts. In some cases no consensus was reached and these points will be mentioned also.

- Levels of evidence I = randomised controlled trials, II= prospective observational robust cohorts, III=animal, experimental or retrospective data).
- We also use the Grade recommendations.
- In opposition to previous consensus, we define now « as high estrogen dose » as the equivalent of 2 mg E2, or 0.625 CEE; « standard» dose as 1 mg E2 or equivalent and « low dose » as 0.5 mg or lower and CEE 0.4mg. Currently, low dose are preferred therapies. For transdermal therapy, the equivalent of 25 µg/d per patch or 1mg/d gel and 3 mg (2 sprays) is considered as low

GRADE for practice guidelines

Grade of recommendation*	Clarity of risk/benefit	Quality of supporting evidence	Implications
1A Strong recommendation High quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	Consistent evidence from well performed randomized, controlled trials or overwhelming evidence of some other form. Further research is unlikely to change our confidence in the estimate of benefit and risk.	Strong recommendation, can apply to most patients in most circumstances without reservation
1B Strong recommendation Moderate quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	Evidence from randomized, controlled trials with important limitations (inconsistent results, methodologic flaws, indirect or imprecise), or very strong evidence of some other form. Further research (if performed) is likely to have an impact on our confidence in the estimate of benefit and risk and may change the estimate.	Strong recommendation, likely to apply to most patients
1C Strong recommendation Low quality evidence	Benefits appear to outweigh risk and burdens, or vice versa	Evidence from observational studies, unsystematic clinical experience, or from randomized, controlled trials with serious flaws. Any estimate of effect is uncertain.	Relatively strong recommendation; might change when higher quality evidence becomes available
2A Weak recommendation High quality evidence	Benefits closely balanced with risks and burdens	Consistent evidence from well performed randomized, controlled trials or overwhelming evidence of some other form. Further research is unlikely to change our confidence in the estimate of benefit and risk.	Weak recommendation, best action may differ depending on circumstances or patients or societal values
2B Weak recommendation Moderate quality evidence	Benefits closely balanced with risks and burdens, some uncertainty in the estimates of benefits, risks and burdens	Evidence from randomized, controlled trials with important limitations (inconsistent results, methodologic flaws, indirect or imprecise), or very strong evidence of some other form. Further research (if performed) is likely to have an impact on our confidence in the estimate of benefit and risk and may change the estimate.	Weak recommendation, alternative approaches likely to be better for some patients under some circumstances
2C Weak recommendation Low quality evidence	Uncertainty in the estimates of benefits, risks, and burdens; benefits may be closely balanced with risks and burdens	Evidence from observational studies, unsystematic clinical experience, or from randomized, controlled trials with serious flaws. Any estimate of effect is uncertain.	Very weak recommendation; other alternatives may be equally reasonable

* GRADE can be implemented with either three or four levels of quality of evidence. UpToDate implements three levels and uses numbers and letters to represent strength of recommendation and quality of evidence respectively.

Definitions

- By estrogen therapy (ET), we mean all systemic estrogen provided orally or parenterally (transdermal, percutaneous, spray). The Estrogen-progestin therapy (EPT) includes regimens combining estrogens and progestins. Hormone (replacement) therapy (HRT or HT), or menopause hormone therapy (MHT) includes all regimens containing steroids for the treatment of menopausal symptoms with inclusion of ET, EPT and tibolone. TSEC consists in the combination of CEE and a SERM. (Bazedoxifene).
- Other routes of administration of estrogens and progestins (vaginal forms, and Intra Uterine delivery Systems) will be discussed separately.
- Other drugs such as SERMS (selective estrogen receptor modulators) also called estrogen agonists-antagonists, SPRM (selective progestin receptors modulators), bone drugs, lipid lowering drugs, androgens, vitamin D, calcium etc. will be discussed separately.

Climacteric symptoms

- Symptoms directly or indirectly related to menopause include :
  - Vasomotor symptoms (hot flushes and night sweats and their consequences)
  - Insomnia
  - Mood changes, psychological symptoms
  - Impaired concentration and memory
  - Sexual dysfunction
  - Urogenital symptoms
  - Arthralgia

Patient information

- Individualised advice is needed. Risks and benefits need to be explained preferably using absolute risk and attribuable estimations.
- Women should also be informed about other health strategies.
- Therapeutic management should be reviewed regularly.
- Shared decision taking should be seeked.

The use of MHT in the following topics have been reviewed

- Premature menopause
- Climacteric symptoms
- Quality of life
- Urogenital atrophy
- Sexual wellbeing
- Osteoporosis
- Breast cancer risk
- Other cancer risks : Colon cancer, Endometrial cancer, Ovarian cancer, lung cancer, others
- Cardiovascular
  - Coronary heart-, stroke, venous thrombo-embolic diseases
- Cognitive function, Alzheimer Disease, Parkinson Disease
- Miscellaneous

Premature and early menopause

- Premature (before 40 years) and early menopause (before 45 years), whether natural or induced, is associated with increased morbidity & mortality, when women are untreated with MHT.
- Several recent meta-analyses reported in particular increased cardiovascular morbi-mortality (Grade 1C)
- Muka T, et al JAMA Cardiol. 2016.

Premature and early menopause

- Data gathered from studies in postmenopausal women aged 50 or more can not necessarily be extrapolated to younger postmenopausal women.
- It is generally recommended to treat these women at least till the normal age of menopause.
- Dosage should be adapted according to symptomatology (*Level 3)*

Climacteric symptoms

- Moderate to severe symptoms disturb women's health-related quality of life for variable (short to very long) durations.
- In women suffering from such symptoms, MHT is the most effective treatment. In these women, it improves their quality of life.
- *(Level of evidence Ia)*

Climacteric symptoms

- Some symptoms are attributed to the climacteric but may result from other etiologies (such as iatrogenic causes).
- In asymptomatic women, MHT usually does not ameliorate objectively the overall quality of life.
- *(level 1b of evidence)*

Mood disturbances

- Menopause transition as well as early menopause may increase vulnerability for some women.
- Mood disturbances and depression as such are not an indication of MHT. However, it may help women who have mood disturbances associated with climacteric symptoms.

Urogenital atrophy

- Vulvo-Vaginal (Urogenital) atrophy occurs (VVA) in up to 70-90% of women. One should systematically inquire whether these symptoms are present. Treatment should encouraged.
- MHT and regular sexual activity improves genital atrophy and its symptoms.
- Local (topical) treatments may be preferred in the absence of other indications,
- Local treatments should be administered for long periods of time (Level 1a) and does not require generally concomitant administration of a progestin.
- Local traetemnt reduces the incidence of recurrent urinary tract infections. (*Level 1b of evidence)*
- Urinary incontinence is not an indication for MHT, although data reported improved urgency using topical estrogen (Level 1b).

Osteoporosis

- Life style counseling (exercise, banishing smoking and alcohol excess, …) is mandatory in all women.
- In vitamin D deprived women (vitamin D < 30 ng/ml) adequate intake vitamin D should be supplied.
- MHT (ET, EPT and Tibolone, TSEC) is efficacious in preventing menopause-related bone loss (level 1a).
- Tibolone and Raloxifene and Basedoxifene prevent vertebral fractures (level 1a) and EPT or ET both hip and vertebral fractures *(Level 1a of evidence)*
- Therefore, MHT may be used in women with high risk of osteoporosis. Since these regimens need to be used for long periods of time, potential long term risks should also be weighed against benefits. Osteoporosis risk can be evaluated by FRAX with BMD and will be discussed separately.
- In established osteoporosis, there is more evidence for using other drugs in the absence of climacteric symptoms (level 2b).

Osteoporosis

- Raloxifene (a SERM) may be used in preventing spinal osteoporosis and fractures as well as invasive breast cancer. It has no proven effect on hip fracture prevention. It increases the incidence of thrombosis (stroke and DVT) and may induce or enhance climacteric symptoms *(level 1b).*
- In 1000 women above the age of 65 years of age, Raloxifene will reduce the incidence of breast cancer per year from 2.7 cases to 1.5 cases (reduction : 1.2 cases). The number of fracture will be reduced from 3.7 to 2.4 fractures per 1000 women per year. The number of thrombosis will increase from 2.7 to 3.9 per 1000 and the number of strokes by 0.7 cases per year. The number of strokes was limited to women with a high 'Framingham Stroke Risk Score'.
- Other SERMS, like Bazedoxifene may have different profiles*:* preventing vertebral osteoporosis and having a neutral effect on breast and endometrium, but increasing probably similarly to other SERMS the thrombosis risk (level 2b) .

- Biphosphonates and denosumab are used in established osteoporosis usually after 60 years old. They have a proven effect also on hip fracture prevention *(level 1a)*.
- These medications need to be combined with adequate calcium and vitamin D intake.
- As for all long term treatments, compliance is essential.
- The long term risk of all used drugs should also be evaluated : a potential concern exists about atrial fibrillation, jaw osteonecrosis and atypical fractures. In women without fractures a drug holiday is generally advised after a few years of treatment. During this time preventive measures and calcium and vitamin D should be maintained (level 1a)

Cardiovascular diseases : CHD

- Experimental and observational studies reported in the past reduced risk of atherosclerosis and CHD in MHT users *(level 2, 3 of evidence).*

- Observational (NHS) and randomised (WHI) data suggest a reduced risk in early menopause (at least before the age of 60 and or less than 10 years after menopause) *(level 1a).* On the other hand, benefit of treatment seems to be lost on CHD risk in women in whom the treatment has been initiated at older age (above the age of 70) (WHI) *(level 1a of evidence).*

Cardiovascular diseases : CHD

- Standard ET doses, used during an average period of 6.8 years, lowered the incidence of CHD in women less than 10 years after menopause (WHI) *(level 1a of evidence).*
- A reduced risk of atherosclerosis has been reported in women starting ET at an early age or soon after menopause *(level 1a)*
- Whether MHT should currently be used for this indication only is currently still debated .

Cardiovascular diseases : CHD

- Standard ET doses, used during an average period of 6.8 years, lower the incidence of CHD in women 50-59 years of age (WHI) *(level 1a of evidence).*
- Some progestins may reduce the beneficial effects of ET (proven for MPA) *(level 1b of evidence).*
- One should be cautious when treating women with high baseline LDL cholesterol levels, since these women seem to be at increased risk of CHD due to MHT.

Cerebrovascular diseases : Stroke

- MHT (EPT, ET and Tibolone) and SERMS increase the risk of stroke *(level 1b of evidence).*
- In the absence of risk factors, the attributable risks are however negligible in women before the age of 60 years.
- At standard dose after 60, there is an excess of 8 to 11 cases /10 000 women- year on a baseline incidence of 26/10 000 women -year.
- Observational studies suggest that low doses MHT confer a lower risk of stroke *(level 2a of evidence).*
- MHT is contraindicated in women with a past history of transient ischemic attack or stroke.
- Individual cardio-vascular risk can be evaluated by risks models.

Venous Thromboembolic diseases (VTE)

- Randomized and observational studies reported that MHT increases the risk of VTE (2 to 3 fold) (level 1b evidence). This means that in a cohort of 1000 women using MHT, an additional 2 cases occur per year of use on a typical baseline risk of 1 per 1000 woman-years.
- Standard ET doses were associated with a rare, but significant increase in VTE (WHI) (0.8 excess/ 1000 women-year). Major identified risk factors are age, overweight, sedentarity and thrombophilia. The risk is highest during the first year of use.
- This risk may be lower using low oral doses of MHT or using MHT regimens with transdermal/percutaneous estrogens (level 2a of evidence).
- Administration of TSEC may be associated with a similar increased risk as MHT.
- The risk may also vary according to type of progestin (lower risk with progesterone and dihydrogesterone)(level 2a)

Breast cancer risk

- Women should be counseled that life style factors influence the breast cancer risk (post-menopausal obesity and alcohol intake increase it and physical exercise decreases it) *(level 1b evidence).*
- Screening for breast cancer should occur whether or not women are using MHT after after informed consent considering pro and con's of screening.
- Some regimens (EPT) increase mammographic density. In women with a high baseline mammographic density, regimens not increasing mammographic density should be favoured such as (TSEC, SERMS, ET, tibolone, and low dose EPT).

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Breast cancer risk

- EPT: Randomized data using one regimen (CEE+MPA) of EPT show an increased risk of breast cancer beyond 5 years of use (WHI) *(level 1b of evidence).*
- This means for example using the WHI data, that in a cohort of 1000 postmenopausal women aged 50-79 years, using EPT the calculated attributable risk of BC is 0,8 additional cases/ year. This additional risk is comparable to that of some life style factors.
- Some observational data show that the excess of relative risk associated with MHT may start earlier and be higher in women with a low BMI. This risk may be different according to the progestin used (lower risk with micronised progesterone, dydrogesterone). Risk is increased over the next 5 years when MHT is initiated shortly after menopause (level 2a of evidence).
- Sequential EPT as well as tibolone, and TSEC may entail lower risk than continuous combined regimens (LIFT) *(level 1b evidence).*

Breast cancer risk

- ET: Standard ET doses, decreased breast cancer incidence in some prospective randomised studies (WHI, DOPS) (level 2a of evidence),but not in all.
- The addition of a progestin is not indicated in hysterectomised women.

Breast cancer risk

- The effect of MHT on the breast cancer risk-related prognosis and mortality is still controversial.

Menopause management of breast cancer patients

- MHT and tibolone are contra-indicated in breast cancer patients (level 1b).
- Hot flushes can be relieved in some patients with clonidine, venlafaxin and GABA-pentin (level 2a). Some SSRIs lower tamoxifen/endoxifen levels but whether it interferes with its efficacy is controversial.
- In hormone-dependent breast cancer patients suffering from vaginal atrophy on aromatase inhibitors, topical non hormonal products should be administered before using topical hormone therapy. If needed, estriol should be preferred *(Level 3).*

Other cancers risks

- Randomized trials report a reduced risk of colon cancer in EPT and tibolone users (but not in the ET users) (level 1 of evidence). Currently, colon cancer prevention is not a recognized indication for HRT.
- Endometrial cancer : ET use is associated with substantially increased risk. Observational data are conflicting as to whether sequential EPT reverses this risk to the baseline risk (level 2 of evidence). However, continuous combined EPT is not associated with increased risk (level 1 of evidence).
- Although some concern has been raised concerning Tibolone (MWS) (level 2 of evidence), a 2 year randomised trial has not shown an increased risk of endometrial pathology (THEBES)(level 1 of evidence).
- TSEC (CEE + Bazedoxifene) has not been associating with an increased endometrium cancer risk.

Other cancer risks

- Observational data reported an increased risk of some ovarian cancer in HRT users, but the attributable risk is in the range of 0.5 case/ 1000 women/ year.
- In smokers older than 60 years, EPT does not increase lung cancer incidence but may increase the related mortality.

Alzheimer's disease and cognitive function

- Observational data showed an impairment of the cognitive function after castration.
- MHT initiated early after menopause may reduce the risk of Alzheimer (level 2).
- It is not proven that MHT prevents/delays Alzheimer's dementia.
- MHT initiated after the age of 65 years increases the risk of dementia (level 1).
- Therefore MHT should currently not be used for this indication.

Good clinical practice

- Life style counselling is essential for preventing and treating cardiovascular diseases, metabolic disorders, breast cancer and osteoporosis.
- Although, in women before 60 years, posthoc analyses of WHI and one meta-analysis report a significant reduced global mortality *(level 1 of evidence)*, the main indication of MHT is climacteric symptoms. In this case, the necessity to alleviate symptoms and the lowest effective dose regimen should be re-evaluated regularly on an individual base. In case of recurrence of symptoms, restarting may be considered, keeping in mind that the absolute risk of MHT related to BC and CVD increases steadily with age.

Good clinical practice

- HT remains a priori, contraindicated in women with a history of stroke and /or BC *(level 1 of evidence)*
- Some experts consider in situ BC and atypical hyperplasia as an absolute contra indication, others as a relative one.
- Similarly, some consider that transdermal, percutaneous and spray ET may be used in women with a history of VTE/ or known thombophilia, but others do not.

Additional remarks

- In case of Hysterectomy, only ET should be used.
- More studies are needed evaluating other regimens, different routes of administration and the use of (micronised) estradiol, progesterone and other progestins, and tibolone which are currently more often used in Europe.

Additional remarks

- In women younger than 60 years, there was a significant decrease in total mortality when data from the ET and EPT (WHI) were combined *(level 1)*

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