MENOPAUSAL HORMONE THERAPY

Definitions

Menopause means the cessation of menses and is determined by the date of the *final menstrual period* (FMP). This diagnosis can only be made retrospectively after 12 consecutive months of amenorrhea after the FMP (1).
The period leading up to the menopause is termed the *perimenopause* or the *menopause transition* (MT).

Menopausal hormone therapy (HT) and *estrogen therapy* (ET) refer to the treatment of the symptoms and risks associated with loss of ovarian hormonal function using sex steroid hormones and analogues.

The median age of the menopause is 51 years, with a range of 45 to 55 years.
Premature menopause is when the onset of menopause occurs prior to age 40; before age 45 it is described as *early menopause* (1).

Symptoms of the menopause

Women may experience a wide range of symptoms during the perimenopause and beyond. These include vasomotor symptoms (VMS); genitourinary syndrome of menopause (GSM); sleep disturbances; loss of libido; skin and hair changes; metabolic changes and weight gain; brain fog, forgetfulness, mood changes/mood swings, depression; muscle aches and joint pain.

The most common of these symptoms are VMS, which around 75% of women will experience. Symptoms may last between 7-10 years (median 7.4 years) while some women may experience them for 10 years or more. Vaginal atrophy is also very common after menopause (2, 3).

Cognitive complaints, especially brain fog, occur frequently and often cause anxiety and a fear of late-onset dementia. Dementia at midlife (before age 64) is, however, rare unless there is a family history of early onset dementia. Data have validated cognitive difficulties during the perimenopause, showing that the most common memory difficulty is with learning and verbal memory; this generally resolves post menopause (6).

Diagnosis

The diagnosis is usually made on clinical grounds, using age, menstrual changes and symptoms. Symptoms caused by an underlying medical issue may mimic menopausal symptoms (e.g. thyroid dysfunction), so testing for other causes may be advised if the clinician is uncertain that these symptoms are caused by lowered estrogen levels (4). In women experiencing symptoms at a young age, without menstrual changes or after hysterectomy, an FSH level of >30 is considered diagnostic of ovarian failure.

Indications for hormone therapy during the perimenopause and after menopause

Hormone therapy is the most effective treatment for the *symptoms* of menopause and specifically for VMS and GSM, and may prevent *bone loss* and fracture (4). Another important indication for HT is *hypoestrogenism* caused by primary ovarian insufficiency (POI) (4), oophorectomy, premature or early menopause. In all these cases HT should continue regardless of symptoms, at least until the median age of menopause, unless there is a specific contra-indication. Data provide convincing evidence that bilateral oophorectomy should be undertaken with caution, due to long-term risks, and that adequate ongoing treatment and monitoring strategies should be in place (9,10).

If HT is started before the age of 60 or within 10 years of the menopause, HT may be effective in reducing *all-cause mortality* by preventing cardiovascular disease (CVD) and hip fractures (4).

Benefits vs. risks of menopausal hormone therapy (HT)

The benefits and risks of HT differ depending on the type, dose, duration of use, route of administration, timing of initiation, and whether a progestogen is used. In women older than 60 years or more than 10 years from the menopause, a careful individualized assessment of the benefit-risk ratio is needed before HT is initiated as the risks of HT use appear greater when initiated later (4). Current insights into benefits and risks are summarized below.

1 ***Symptom relief.*** HT is effective, beneficial and indicated for the treatment of moderate to severe VMS, and moderate to severe symptoms of GSM. It also helps to improve sleep directly (micronised progesterone) and by reducing night sweats and may improve sexual function when atrophic vaginitis is improved (4).

2 ***Bone and muscle.*** Systemic HT is effective to prevent postmenopausal osteoporosis and reduce fracture risk. It is considered appropriate to use for this indication in postmenopausal women without osteoporosis, younger than 60 years or within 10 years of menopause (4). Antiresorptive medications are preferable as treatment for established postmenopausal osteoporosis. Sarcopenia and osteoporosis may occur due to ageing and loss of estrogen in the menopause transition. Some data suggest that exercise plus ET may prevent loss of muscle mass, strength and performance (4).

3 ***Gastro-intestinal and metabolism.*** The incidence of new onset type 2 diabetes mellitus is significantly reduced by systemic HT. HT may be beneficial for glycemic control in women with preexisting type 2 diabetes mellitus and is not contra-indicated (4). Estrogen use appears to increase the risk of gall stones and cholecystitis (4).

4 ***Cognition.*** VMS, sleep disturbance and mood changes influence cognition (7) and it is intuitive that treating these symptoms will improve cognition. The clinical approach to cognitive issues and the risk for dementia should, however, focus on modifiable risk factors such as obesity, hypertension, diabetes, physical activity, smoking, cognitive activities, appropriate treatment of depression and avoidance of social isolation (6). Treatment with ET in oophorectomised women, and those with premature or early menopause, is indicated at least to the typical menopausal age to reduce cognitive decline. Oophorectomized women not treated with ET have a greater risk of cognitive decline or dementia 30 years later, compared to women treated with ET immediately post-surgery and until at least age 50 years (8).

5 ***Cardiovascular disease (CVD).*** The effect of HT on CVD seems to vary according to the timing of HT initiation, referred to as the "window of opportunity" or the timing hypothesis for treatment. This hypothesis suggests that the CVD benefits outweigh the risks when HT is initiated early in menopause in younger, healthy women. When HT is initiated years later and possibly after the onset of significant atheroschlerosis, the CVD risks usually outweigh the potential benefits (11). HT in recently postmenopausal women had a positive or neutral effect on subclinical atherosclerosis progression and coronary artery calcification in randomised controlled trials (4).

6 ***Venous thromboembolism (VTE).*** Oral HT may increase the risk for spontaneous or elicited VTE, especially in the first year of treatment. Obesity, older age at onset of treatment and higher doses increase the risk. The risk is related mostly to estrogen, but progestogen can also contribute. Micronised progesterone is probably less thrombogenic than other progestogens, and transdermal HT has not been associated with VTE risk in observational studies (12).

7 ***Breast cancer.*** The effect of HT on breast cancer risk depend on the type and dosage of hormone therapy, duration of use, prior exposure and individual characteristics. There may also be different effects on incidence, stage at diagnosis, on tumour behavior and cancer survival. Estrogen-only HT seems to have a limited effect on the risk to develop breast cancer and the current consensus is that it does not significantly increase or decrease breast cancer risk.

On the other hand, there is Level I evidence that the addition of a progestogen to estrogen as part of systemic menopausal hormone therapy increases the risk of breast cancer. Preclinical and observational studies show that natural micronized progesterone or dydrogesterone may be safer than other synthetic progestogens resulting in a neutral effect on breast cancer risk when used for up to 5 years and a lower risk of breast cancer than other synthetic progestins if used beyond 5 years (8). Observational evidence suggests that HT use does not further increase the risk of breast cancer in women with a family history of breast cancer or for peritoneal cancer after bilateral salpingo-oophorectomy for BRCA 1 & 2 genetic variants (13).

Women should be counselled about breast cancer risk with HT, putting the data into perspective: the risk for combined HT is similar to that of modifiable risk factors such as two alcoholic beverages daily, obesity and low physical activity. HT is not advised for survivors of breast cancer, but low dose vaginal estrogens may be considered in consultation with the attending oncologist if bothersome menopausal genitourinary symptoms persist after a trial of non-hormonal options (lubricants and moisturisers) (4).

8 ***Endometrial cancer.*** Unopposed ET increases the risk for uterine malignancies in women with an intact uterus and long-term use is therefore contra-indicated. Intra-uterine progestogen is considered to be a safe option to oppose systemic estrogen. Opposed HT generally has a neutral or negative effect on endometrial cancer risk, depending on dosage. Use of HT is an option for treatment of menopausal symptoms in women with surgically treated, early stage low grade endometrial cancer in consultation with the oncologist, but is not advised with high risk, high grade or advanced stage endometrial cancer or endometrial stromal cell sarcomas or leiomyosarcoma. (4)

9 ***Ovarian cancer.*** Current and recent use of HT is associated with a small but statistically significant increased risk of ovarian cancer in observational studies, principally for the serous type. Use of HT is not advised in women with hormone dependent ovarian cancers, including endometroid, granulosa cell tumours and low-grade serous carcinomas (14).

10 ***Other cancer.*** Observational studies show a reduced incidence of colorectal cancers in current HT users with reduced mortality (4) There appears to be an overall neutral effect of HT on lung cancer incidence and survival (4)

Choice of product

Estrogen only systemic therapy (ET) may be used in those women who are symptomatic, do not have a uterus and without a history of severe endometriosis. In all other women needing progestogen the progestogen can be added systemically or as a progestogen IUS. The risk of breast cancer seems to be related to progestogen type, days, and dosage.

Transdermal HT may be advantageous for women with an elevated thrombotic risk and is preferred by others. In general, patches and gels have similar pharmacokinetics; gels have the advantage of less adhesive side-effects, while patches have steady plasma levels. Low dose vaginal ET formulations are effective and safe to treat GSM on its own or in combination with systemic therapy. Systemic absorption is minimal, additional progestogen therapy is not needed, and this treatment is considered safe for breast cancer survivors without active disease.

Follow-up and duration of use

During follow-up of the menopausal patient, ongoing risk assessment should be done, with a focus on gynaecologic disease, risks and symptoms; bone, breast and cardio-vascular risk factors. Long term use of HT for longer than 10 years needs an ongoing audit of benefits versus risks, but there is no clearly determined cessation date.

The increased risks of HT in older women are related to late initiation and not to continued use in those who started at the time of menopause. Over time, dose reduction and a change to the non-oral route of administration can be considered to further ameliorate these risks.

Compounded bioidentical hormone therapy

'Bioidentical' is a marketing term used to describe exogenous hormones which are similar to endogenous hormones. "Compounded" is a term used to describe the mixing of these hormone gels or similar by a pharmacy.

Compounded bio-identical HT is marketed as safe, natural and superior to conventional, pharmaceutical-grade HT and are marketed as having 'anti-ageing' effects. Compounded BHTs are not tested for quality, safety and negative side effects and do not contain the requisite pharmaceutical information label describing risks and side effects. Dosage is often based on salivary, serum and urine hormone level testing; these are however unreliable and not recommended.

There is a wide range of well-regulated HT available containing body identical hormones in many different formations such as tablets, transdermal patches, gels or vaginal treatments. The routine use of compounded bioidentical hormone therapy is not recommended due to safety concerns, minimal government regulation and monitoring, overdosing, underdosing, presence of impurities and lack of sterility, lack of scientific efficacy and safety data, and lack of a label outlining risks.(4) Serum hormone testing is rarely needed, as bleeding patterns are the gold standard method to diagnose menopausal stage (10). Compounded bioidentical hormones can be considered in patients with allergies to ingredients in approved products or where there is unavailability of dosages or medications (off-label use) (4,16)

This document was adapted from the South African Menopause Society guideline, and is endorsed by SASOG as part of the BetterGYN® programme.

References available on request.

Writing team: Dr S Percy Moodley & Dr Nicole Jaff **Contributions & review**: BetterGYN team

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Clinical Guideline

This document is intended to guide clinical care without changing the responsibility of the health care team or the patient.
It never replaces clinical judgement and individualised care.

Developed and endorsed by SASOG as part of the BetterGyn® programme