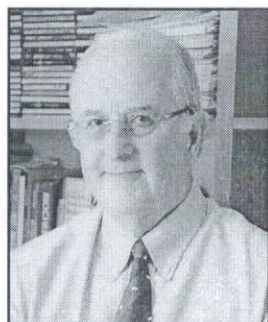


New menopause guidelines

IMPLICATIONS FOR SOUTH AFRICAN CLINICIANS

Introduction



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"Menopause impacts negatively on a woman's quality of life and her economic contribution to our society" – Professor Alan Alperstein

The UK National Institute for Health and Care Excellence (NICE)'s new guidelines for women undergoing menopause¹ provide some useful clinical tools for South African clinicians, according to Professor Alan Alperstein, of UCT and Kingsbury Hospital, Cape Town.

These guidelines, like the South African guidelines,² focus on an individualised approach to menopause treatment. The South African guidelines, last published in 2014, are also patient orientated with the recommendation that therapy choices be a joint decision between the healthcare provider and an informed patient, based on her current clinical status and evidence-based medicine.

When considering the health costs of treating menopausal symptoms, the reduced productivity of women undergoing menopause needs to be taken into account.³ "This is particularly true in our society today, where women are key to the productiveness of many sectors of our economy," Professor Alperstein noted.

Clinicians need to spend time assessing the extent of symptoms in individual patients, informing them of the benefits and risks of therapy. The NICE guidelines again emphasise that for most women, hormone therapy (HT) is a very effective treatment for vasomotor symptoms, such as hot flushing, and also reduces the risk of osteoporotic fractures.

A Diagnosis of perimenopause and menopause

The diagnosis of the advent of the menopause is based on clinical evaluation of symptoms, with the following key clinical insights:

1. Diagnose perimenopause in otherwise healthy women aged over 45 years, based on vasomotor symptoms and irregular periods, but without laboratory tests.
2. Diagnose menopause in women over the age of 45 years who have not had a period for at least 12 months and are not using hormonal contraception, but without laboratory tests.

3. Diagnose menopause in women without a uterus over the age of 45 years based on symptoms and without laboratory tests.
4. Take into account that it can be difficult to diagnose menopause in women who are taking hormonal treatments, for example for the treatment of heavy periods!
5. Use a follicle stimulating hormone (FSH) test in women younger than 45 years with menopausal symptoms and in younger women under 40 years in whom menopause is suspected.

Professor Alperstein points out that this emphasis on limiting FSH tests in the NICE guidelines is with a view to achieving savings in the health sector. "In my view this is not an issue, if FSH tests are used properly. I use FSH tests to help prove to doubting patients that they are indeed menopausal and to introduce to younger symptomatic patients the concept that ovarian function is declining." It is important to note that the FSH test is not essential to the diagnosis of the menopause in women older than 45 years with symptoms.

In the younger symptomatic woman, two FSH tests should be done, 4-6 weeks apart, to make the diagnosis of premature ovarian insufficiency (POI), which will be dealt with separately in section D.

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B Managing menopausal symptoms

The new NICE guidelines recommend HT for menopausal symptoms after discussing the short-term (up to five years) and longer-term benefits and risks. A combination of estrogen and progestogen is recommended for women with a uterus while for women who have had a hysterectomy, estrogen alone is recommended. Tibolone is recommended for women with a uterus as well as women who have had a hysterectomy. Tibolone offers similar clinical benefits and risks to other estrogen and progestogen formulations.

The exception to this treatment approach is in women with POI.

C Long-term benefits and risks of HT

"When prescribing HT, it is vital to relate the risk of use to the situation of the individual patient in front of you. The new NICE guidelines provide useful tables for the clinician to simplify in discussion with patients," Professor Alperstein said.

Risk of cardiovascular disease

The NICE guidelines point out that the presence of cardiovascular risk factors is not a contraindication to HT as long as these risks are being addressed; neither does HT increase cardiovascular disease risk when started in women aged under 60 years. Table 1 provides data summarising the *absolute* rates of coronary heart disease (CHD) for different types of HT, while Table 2 addresses the stroke rate per 1 000 women users of HT over a 7.5 year period.

Risk of breast cancer

The principle should be noted from the outset that the baseline risk of breast cancer for women around menopausal age varies according to underlying risk factors. HT with estrogen alone is associated with little or no change in risk while estrogen plus progestogen can be associated with an increase in the risk of breast cancer (Table 3).

Table 1: Absolute rates of CHD for different types of HT compared with no HT (or placebo)*

Difference in CHD incidence per 1000 women over 7.5 years		
Women on estrogen only	Current users	>5 years since stopping
RCT	6 fewer	6 fewer
Observational data	6 fewer	–
Women on estrogen and progestogen	Current users	>5 years since stopping
RCT	5 more	4 more
Observational data	–	–

– There are no available data in this category

RCT – randomised clinical trial

*Simplified from NICE guidelines

Observational – is based on cohort studies with several thousand women

Table 2: Difference in stroke incidence per 1000 women on HT over 7.5 years

Women on estrogen only	Current users	>5 years since stopping
RCT	0	1 more
Observational data	3 more	–
Women on estrogen and progestogen	Current users	>5 years since stopping
RCT	6 more	4 more
Observational data	4 more	–

– There are no available data in this category

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Table 3: Absolute rates of breast cancer for different forms of HT compared with no HT, different durations of HT use and time since stopping

Difference in breast cancer incidence per 1000 women over 7.5 years				
Women on estrogen only	Current users	Treatment <5 years	Treatment 5-10 years	>5 years since stopping
RCT	4 fewer	–	–	5 fewer
Observational data	6 more	4 more	5 more	5 fewer
Women on estrogen and progestogen	Current users	Treatment <5 years	Treatment 5-10 years	>5 years since stopping
RCT	5 more	–	–	8 more
Observational data	17 more	12 more	21 more	9 fewer

– There are no available data in this category

Benefits in osteoporosis

The baseline population risk of fragility fractures in South Africa is not known; nonetheless HT is effective in decreasing the incidence of fractures in patients at both high and low risk of fractures as they age. In some patients, a degree of fracture prevention persists after cessation of HT, but in many patients bone-sparing medication will be needed.

D Managing POI

“This is an often misdiagnosed condition and, when identified, it is poorly treated,” Professor Alperstein noted.

In the NICE guidelines, the management of POI emphasises the importance of starting hormonal treatment either with HT or a combined hormonal contraceptive and continuing treatment until at least the age of natural menopause.

The principles of treatment that apply to women undergoing a natural menopause in their 50s are not applicable to young women with POI.

POI needs sympathetic and supportive handling. It is far more reasonable to place these younger women on a combined oral contraceptive (COC) than conventional HT. One then transitions these women onto HT from COC at the appropriate age.

SOUTH AFRICAN RESEARCH ON WOMEN'S EXPERIENCE OF MENOPAUSE – NEED FOR CLINICAL EDUCATION AT DIAGNOSIS

There is still a lack of published information on South African women's attitudes to and experience of menopause and its treatment. If you have data that you wish to share with deNovo Medica readers, please contact info@denovomedica.com

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The World Health Organisation estimates that 76% of post-menopausal women will be living in developing countries by 2030.

A study undertaken 10 years ago in private practice in women of middle-to-high

socioeconomic status⁴ in the Western Cape found that these women were well informed about the menopause and treatment with HT. A significant number of patients surveyed had been on HT for

more than 10 years. Their most important reason for initiation of HT was vasomotor symptoms (70%) and 10% were aware of the skeletal protection of HT.

In contrast, in the same time period, a study of rural Xhosa women⁵ showed that they experienced the menopause at a comparable age to their urban Caucasian counterparts. Despite a high incidence of vasomotor symptoms, they were not aware of the potential benefits of HT. These research initiatives were largely stimulated by the publication of the WHI study (2002), when clinicians needed to re-evaluate their stance on hormonal therapy.

Subsequently, there has been a paucity of data on African women's experience of the menopause. The Study of Women's Health across the Nation (SWAN) study⁶ in the USA showed that African-American and Hispanic women had particularly persistent vasomotor systems lasting an average of 10 years compared to the median duration of 6.5 years in their white counterparts.

A recent evaluation of techniques⁷ to stage the menopausal transition in sub-Saharan African women provides pointers to a different current experience of women resident in Soweto (Source study: Birth to Twenty Plus Cohort).

The median age of final menstrual period (FMP) was 49 years, somewhat younger than in western women. Defining features of the menopause was vasomotor symptoms, sexual problems in early

menopause and irritability in late menopause. Obesity was strongly related with more severe vasomotor symptoms. HIV was judged to have no effect on menopause symptoms.

Of great importance was the fact that 50% of the cohort did not understand the meaning of the term 'menopause', but were able to give reasonably precise information about changes in bleeding patterns. Primary care practitioners need to ask about vasomotor symptoms, irritability and other factors (such as sleeping patterns) that can affect women in this age group in order to assess whether the menopausal transition is affecting the patient's quality of life.

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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).



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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 atherosclerosis, 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.



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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 endometrioid, 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.



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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.

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