

Updated IMS recommendations on postmenopausal hormone therapy and preventive strategies for midlife health

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INTRODUCTION

The past decade has seen marked fluctuations in opinions concerning the merits and risks of postmenopausal hormone replacement therapy (HRT). In July 2002, menopause management faced a major turning point when the first data from the Women's Health Initiative (WHI) trial were released. This study was categorized as a primary prevention trial for coronary heart disease. However, the mean age at recruitment was 63 years, when menopausal symptoms have usually finished and HRT is rarely started, but this important difference from common clinical practice was not acknowledged at that time. Instead, WHI investigators concluded that HRT was not cardioprotective and that its risk–benefit ratio did not favor the use of postmenopausal hormones for prevention of chronic diseases. As a result, there was a dramatic change in prescription habits following recommendations to reserve HRT for very symptomatic women, and to limit its use to the 'shortest duration needed' and to 'the lowest effective dosage'. This was the atmosphere in which the International Menopause Society (IMS) initiated a Workshop held in Vienna (December 2003) and produced the subsequent IMS Position Paper resulting from the Workshop discussions. Basically, the IMS did not accept some interpretations attributed to the WHI results and, being independent of local or regional constraints imposed by official health authorities, called for a more balanced approach to the scientific data. Because additional information has been accumulated from both arms of the WHI study, from observational trials and from other studies during the following years, the first IMS Statement was updated in 2007, enlarging its scope to menopause management and adult women's health in general. This revised Statement was formulated in a Workshop held in Budapest in February 2007, in which 30 experts from the various fields of menopause medicine presented the latest information and delegates from 60 National and Regional

Menopause Societies from all continents participated in the discussions.

The 2011 revision of the IMS Recommendations is published when the atmosphere around the issue of postmenopausal HRT is much more rational. The pendulum swung back from its peak negative sentiment following more detailed data from the WHI study that demonstrated the importance of the age at initiation and the good safety profile of HRT in women younger than 60 years. Since these were exactly the IMS views expressed in the previous Recommendations, the current update is similar in principle to the 2007 version, but with the additional clinical data where needed. It has been produced by a small Writing Group of experts, and not from a formal workshop, but is the considered view of the IMS on the principles of HRT in the peri- and postmenopausal periods. Throughout the Recommendations, the term HRT will be used to cover therapies including estrogens, progestogens, combined therapies, androgens and tibolone. The IMS is aware of the geographical variations related to different priorities of medical care, different prevalence of diseases, and country-specific attitudes of the public, the medical community and the health authorities toward menopause management, different availability and licensing of products, all of which may impact on HRT. These Recommendations and the subsequent key messages therefore give a global and simple overview that serves as a common platform on issues related to the various aspects of hormone treatment, which could be easily adapted and modified according to local needs.

GOVERNING PRINCIPLES

Consideration of HRT should be part of an overall strategy including lifestyle recommendations regarding diet, exercise, smoking cessation and safe levels of alcohol consumption for maintaining the health of peri- and postmenopausal women.

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HRT must be individualized and tailored according to symptoms and the need for prevention, as well as personal and family history, results of relevant investigations, the woman's preferences and expectations. The risks and benefits of HRT differ for women during the menopause transition compared to those for older women.

HRT includes a wide range of hormonal products and routes of administration, with potentially different risks and benefits. Thus, the term 'class effect' is confusing and inappropriate. However, evidence regarding differences in risks and benefits between different products is limited.

Women experiencing a spontaneous or iatrogenic menopause before the age of 45 years and particularly before 40 years are at higher risk for cardiovascular disease and osteoporosis and may be at increased risk of affective disorders and dementia. Use of HRT may reduce these risks but the evidence for this is limited. HRT may reduce symptoms and preserve bone density and is advised at least until the average age of menopause.

Counselling should convey the benefits and risks of HRT in clear and comprehensible terms, e.g. as absolute numbers rather than, or in addition to, percentage changes from baseline expressed as a relative risk. This allows a woman and her physician to make a well-informed decision about HRT. Written information about risks and benefits as well as decision aids may be useful.

HRT should not be recommended without a clear indication for its use, i.e. significant symptoms or physical effects of estrogen deficiency.

Women taking HRT should have at least an annual consultation to include a physical examination, update of medical and family history, relevant laboratory and imaging investigations, a discussion on lifestyle, and strategies to prevent or reduce chronic disease. There is currently no indication for increased mammographic or cervical smear screening.

There are no reasons to place mandatory limitations on the duration of HRT. Whether or not to continue therapy should be decided at the discretion of the well-informed woman and her health professional, dependent upon the specific goals and an objective estimation of ongoing benefits and risks.

Dosage should be titrated to the lowest effective dose. Lower doses of HRT than have been used previously may reduce symptoms sufficiently and maintain quality of life for many women. Long-term data on lower doses regarding fracture or cancer risks and cardiovascular implications are still lacking.

In general, progestogen should be added to systemic estrogen for all women with a uterus to prevent endometrial hyperplasia and cancer. However, natural progesterone and some progestogens have specific beneficial effects that could justify their use besides the expected actions on the endometrium, e.g. the well-documented blood pressure-lowering effect of drospirenone. Also, progestogens may not be alike in regard to potential adverse metabolic effects or associated breast cancer risk when combined with long-term estrogen therapy. Low-dose vaginal estrogens, administered for the relief of urogenital atrophy, are systemically absorbed,

but not at levels that stimulate the endometrium, and so concurrent progestogen is not required. Direct delivery of progestogen to the endometrial cavity from the vagina or by an intrauterine system does provide endometrial protection and may cause less systemic progestogenic effects than other routes of administration.

Androgen replacement should be reserved for women with clinical signs and symptoms of androgen insufficiency. Androgen replacement often has significant beneficial effects in women with bilateral oophorectomy or adrenal failure, particularly on health-related quality of life and sexual function.

BENEFITS OF HRT

General

HRT remains the most effective therapy for vasomotor symptoms and urogenital atrophy. Other menopause-related complaints, such as joint and muscle pains, mood swings, sleep disturbances and sexual dysfunction (including reduced libido) may improve during HRT. Quality of life and sexual function may also improve. The administration of individualized HRT (including androgenic preparations when appropriate) may improve both sexuality and overall quality of life.

Postmenopausal osteoporosis

HRT is effective in preventing bone loss associated with the menopause and decreases the incidence of all osteoporosis-related fractures, including vertebral and hip fractures, even in women not at high risk of fracture. Based on evidence of effectiveness, cost and safety, HRT can be considered as one of the first-line therapies for the prevention and treatment of osteoporosis in postmenopausal women, younger than 60 years, with an increased risk of fracture. The initiation of HRT for the sole purpose of the prevention of fractures after the age of 60 years is not recommended. Continuation of HRT after the age of 60 years for the sole purpose of the prevention of fractures should take into account the possible long-term effects of the specific dose and method of administration of HRT, compared to other proven non-hormonal therapies.

The protective effect of HRT on bone mineral density (BMD) declines after cessation of therapy at an unpredictable rate, although some degree of fracture protection may remain after cessation of HRT. If the patient is still considered at risk for fracture after cessation of HRT, additional therapy with proven bone-sparing medication should be given.

Evidence of the fracture-protective effect of HRT is limited to standard dosages of conjugated equine estrogen (CEE) and medroxyprogesterone acetate (MPA), given by the oral route. Evidence for protection against loss of BMD is available for lower than standard doses in oral (CEE and 17β -estradiol) and transdermal (17β -estradiol) administration. Tibolone, a synthetic molecule that has affinity for the estrogen, progesterone and androgen receptors, has proven efficacy

against vertebral and non-vertebral fractures. The selective estrogen receptor modulators (SERMs), raloxifene, lasofoxifene and bazedoxifene, reduce the risk of vertebral fracture in postmenopausal women with or without prevalent vertebral fractures.

Cardiovascular disease

Cardiovascular disease is the principal cause of morbidity and mortality in postmenopausal women. Major primary prevention measures (besides smoking cessation and diet control) are weight loss, blood pressure reduction, regular exercise and diabetes and lipid control. HRT has the potential for improving the cardiovascular risk profile through its beneficial effects on vascular function, cholesterol levels, glucose metabolism and blood pressure.

There is evidence that estrogen therapy may be cardioprotective if started around the time of menopause and continued long term (often referred to as the ‘window of opportunity’ concept). HRT reduces the risk of diabetes and, through improving insulin action in women with insulin resistance, it has positive effects on other related risk factors for cardiovascular disease such as the lipid profile and metabolic syndrome.

In women less than 60 years old, recently menopausal and without evidence of cardiovascular disease, the initiation of HRT does not cause early harm and may reduce morbidity and mortality from coronary heart disease. Continuation of HRT beyond the age of 60 years should be decided as a part of the overall risk–benefit analysis.

Initiation of HRT in elderly women or those who are more than 10 years postmenopause may be associated with increased risk for coronary events, mainly in the first 2 years of use. It is therefore not recommended to initiate HRT beyond the age of 60 years solely for the purpose of primary prevention of coronary artery disease. Also, it is well accepted that initiation of HRT is not appropriate in the routine treatment of older women with coronary disease.

Other benefits

Systemic HRT and especially local estrogen can correct estrogen deficiency changes in the urogenital tract and maintain vaginal health. HRT has benefits for connective tissue, skin, joints and intervertebral disks. Combined CEE + MPA for more than 4 years may reduce the risk of colon cancer. HRT initiated around the time of menopause or in younger postmenopausal women is associated with a reduced risk of Alzheimer’s disease.

POTENTIAL SERIOUS ADVERSE EFFECTS OF HRT

Studies on the risks of postmenopausal hormone use have mainly focused on breast and endometrial cancer, venous

thromboembolism (pulmonary embolism or deep vein thrombosis), stroke and coronary events.

Breast cancer

The incidence of breast cancer varies in different countries. Therefore, currently available data may not be applicable everywhere. The degree of association between breast cancer and postmenopausal HRT remains controversial.

Women should be reassured that the possible increased risks of breast cancer associated with HRT are small (less than 0.1% per annum, or an incidence of <1.0 per 1000 women per year of use), and less than the increased risks associated with common lifestyle factors such as obesity and alcohol consumption. Randomized controlled data from the WHI study demonstrated no increased risk in first-time users of HRT during the 5–7 years since initiation of treatment. The majority of subjects in the WHI study were overweight or obese, which may have affected their basal breast cancer risk.

Data from the WHI and the Nurses’ Health Study suggest that long-term, estrogen-only administration for 7 and 15 years, respectively, does not increase the risk of breast cancer in North American women. Recent European observational studies suggest that the risk may increase after 5 years.

The concomitant dramatic decrease in HRT use and the immediate reduction in breast cancer incidence post-WHI in some studies were presented as further proof of the carcinogenic effect of estrogen; however, recent data indicate an increase in breast cancer incidence despite stabilization in the number of HRT users, suggesting that HRT may be a promoter of an existing breast tumor rather than an initiator of cancer.

There are insufficient data to evaluate the possible differences in the incidence of breast cancer using different types, doses and routes of estrogen, natural progesterone and progestogens and androgen administration. Nevertheless, large European observational studies suggest that a difference in risk between estrogen-only and combined estrogen–progestogen therapy is seen with some categories of progestogens but not with natural progesterone derivatives.

Baseline mammographic density correlates with breast cancer risk. This does not necessarily apply to the increase in mammographic density induced by HRT. The combined estrogen–progestogen therapy-related increase in mammographic density may impede the diagnostic interpretation of mammograms.

Endometrial cancer

Unopposed estrogen administration induces a dose-related stimulation of the endometrium. Women with a uterus should have progestogen supplementation to counteract this effect.

Continuous combined estrogen–progestogen regimens are associated with a lower incidence of endometrial hyperplasia and cancer than occurs in the normal population.

Direct intrauterine delivery systems may have advantages. Regimens containing low-/ultra-low-dose estrogen and progestogen cause less endometrial stimulation and less bleeding.

Long-cycle regimens and long-term use of monthly sequential regimens do not provide optimal endometrial protection.

SERMs other than tamoxifen do not stimulate the endometrium and do not increase the incidence of endometrial spotting or bleeding compared to women not using any hormonal therapy.

Thromboembolism and cardiovascular events

The HRT-related risk for serious venous thromboembolic events increases with age (although minimal in low-risk women until age 60), and is also positively associated with obesity and thrombophilia. Transdermal estrogen may avert the risk associated with oral HRT by avoiding first-pass hepatic metabolism. The impact on the risk of a thromboembolic event may also be affected by the type of progestogen.

The risk of stroke is correlated with age, but stroke is a rare event before age 60. HRT may further increase that risk, becoming significant after the age of 60. Low-dose transdermal preparations are not associated with increased risk for stroke. Safety data from studies of low-dose and ultra-low-dose regimens of estrogen and progestogen are encouraging, with fewer adverse events, but data from large prospective trials are awaited.

ALTERNATIVE TREATMENTS

The efficacy and safety of complementary alternative medicines have not been demonstrated and further studies are required.

Selective serotonin reuptake inhibitors (SSRI), selective noradrenaline reuptake inhibitors (SNRI) and gabapentin are effective in reducing vasomotor symptoms in short-term studies. Their long-term safety needs further evaluation.

There are no medical or scientific reasons to recommend unregistered 'bioidentical hormones'. The measurement of hormone levels in the saliva is not clinically useful. These 'customized' hormonal preparations have not been adequately tested in studies and their purity and risks are unknown.

RESEARCH

There is urgent need for further research especially into the risks and benefits of lower doses, regimens and routes of administration of HRT, and into late-life cognitive effects of midlife HRT use.

CONCLUSIONS

Postmenopausal HRT is not a single regimen given to a standard woman. The benefits and risks vary greatly in

individual circumstances, but research over the last decade has helped to show that risks can be minimized and benefits maximized with selection of the optimal regimen at the optimal time.

The safety of HRT largely depends on age. Healthy women younger than 60 years should not be unduly concerned about the safety profile of HRT. New data and re-analyses of older studies by women's age show that, for most women, the potential benefits of HRT given for a clear indication are many and the risks are few when initiated within a few years of menopause.

The WHI and other studies strongly suggest that it is the progestogen component of HRT that is more significant in any increase in breast cancer risk rather than the estrogen. Thus, it seems prudent to minimize progestogen use where safely possible and, in the near future, progestogens may be replaced by SERMs that do not adversely affect the breast but also inhibit endometrial proliferation.

There is increasing evidence that non-oral routes of estrogen or tibolone have little or no increased risk of thromboembolism and would be the regimens of choice in women with thromboembolic risk factors, if HRT was considered appropriate.

There is mounting evidence from laboratory, animal, observational studies and randomized controlled trials of a therapeutic window of benefit for long-term cardioprotection and neuroprotection if HRT is prescribed in midlife from near menopause in symptomatic women.

Women can have the option of HRT for as long as they derive symptomatic benefit and are aware of the risks for their regimen and personal circumstances. They can try without HRT every few years, but menopausal symptoms in some women can last for many years and should be treated with the lowest effective dose.

It is very unlikely that long-term, randomized, controlled trials, like the WHI which finished prematurely, will ever be funded or be practically possible in the future. Therefore, clinicians in any field must treat or not treat on the balance of the available data. Such data for the foreseeable future have and will come from short-term, randomized trials using surrogate endpoints for long-term morbidities (e.g. The Kronos Early Estrogen Prevention Study (KEEPS) and the Evaluation of Losartan In The Elderly (ELITE) study), or from long-term, non-randomized cohort studies (e.g. the Nurses' Health Study), or from systematic reviews of the quality literature.

The excessive conservatism engendered by the presentation to the media of the first results of the WHI in 2002 has disadvantaged nearly a decade of women who may have unnecessarily suffered severe menopausal symptoms and who may have missed the potential therapeutic window to reduce their future cardiovascular, fracture and dementia risk.

These IMS evidence-based recommendations are intended to encourage better care of all women in midlife.

KEY MESSAGES

EXERCISE IN THE MENOPAUSE

- Regular exercise reduces cardiovascular and total mortality.
- Better metabolic profile, balance, muscle strength, cognition and quality of life are observed in physically active persons. Heart events, stroke, fractures and breast and colon cancers are significantly less frequent.
- The benefits of exercise far outweigh possible adverse consequences: the more, the better, but too much may cause harm.
- Optimal exercise prescription is at least 150 minutes of moderate-intensity exercise per week. Two additional weekly sessions of resistance exercise may provide further benefit. However, the recommended intensity of aerobic activity should take into account the older adult's aerobic fitness.

HEALTHY LIFESTYLE

- Obesity (body mass index $> 30 \text{ kg/m}^2$) affects over 20% of the population in many parts of the world and is becoming an increasing problem in the lower socioeconomic sectors and also among children.
- Weight loss of only 5–10% is sufficient to improve many of the abnormalities associated with the insulin resistance syndrome.
- The basic components of a healthy diet are: several servings/day of fruits and vegetables, whole grain fibers, fish twice per week, and low total fat (but the use of olive oil is recommended). Consumption of salt should be limited and the daily amount of alcohol should not exceed 30 g for men and 20 g for women.
- Smoking should be prohibited.
- Lifestyle modifications include socializing, and being physically and mentally active.
- The public health approach to lifestyle promotion requires a multidisciplinary approach, starting from schools through to work places, involving the food and advertising industry, as well as medical insurers and health authorities. A new paradigm in the doctor–patient relations is required, where the doctor becomes more of an advisor and the patient has to take the responsibility for his/her own health.

UROGYNECOLOGY

- Symptoms such as vaginal dryness, soreness, dyspareunia, urinary frequency, nocturia and urgency are extremely common in postmenopausal women. The prevalence of incontinence in women increases with age. Overall, 25% of women report urinary incontinence of which 7%

consider it to be significant; 50% of women complain of stress incontinence, 11% urgency incontinence and 36% mixed incontinence.

- There is a wide variation in symptoms and signs of urogenital aging.
- The loss of lubrication and hormonal changes may lead to sexual dysfunction. Treatment of this condition improves quality of life, not only for the woman but also for her partner.
- Urogenital symptoms respond well to estrogens. Long-term treatment is often required as symptoms can recur on cessation of therapy. Systemic risks have not been identified with local low-potency/low-dose estrogens.
- Use of systemic HRT does not seem to prevent urinary incontinence and is not preferable to low-dose local estrogens in the management of urogenital atrophy or recurrent lower urinary tract infections.
- After lifestyle changes and bladder retraining, antimuscarinic drugs combined with local estrogens constitute first-line treatment in postmenopausal women with symptoms suggestive of an overactive bladder.
- All women complaining of stress urinary incontinence will benefit from pelvic floor muscle training in the first instance. Duloxetine may work synergistically with conservative therapy. However, many women will ultimately undergo surgery, and retropubic and transobturator tapes are the most popular procedures.
- There is currently no role for systemic estrogen therapy in women with pure stress urinary incontinence.

OSTEOPOROSIS

General guidelines

The disease

- Osteoporosis is a systemic skeletal disease of diminished bone strength that results in fractures when falling from one's own body height. Bone strength is determined by a combination of bone density and microarchitectural integrity.
- Postmenopausal osteoporosis can be caused by the failure to attain peak bone density or accelerated bone loss after menopause.
- Although skeletal health is a function of genetic predisposition, it can be modified by lifestyle factors such as diet, weight-bearing exercise and the avoidance of bone-toxic substances.
- Hip fracture is responsible for a large proportion of the financial burden of osteoporosis to health-care systems but other osteoporosis-related fractures, particularly vertebral fractures, cause considerable morbidity which can be long-standing.

Diagnosis and assessment

- The diagnosis of osteoporosis is based on BMD assessment by dual X-ray absorptiometry (DXA), expressed as the *T*-score, or the presence of fragility fractures.
- BMD is not a cost-effective population screening tool but is best applied on a selective basis, based on age and other risk factors.
- The 10-year probability of fracture in an individual can be estimated using a model that integrates various risk factors for fracture, such as the FRAX model developed through the World Health Organization, which is available online at www.sheffield.ac.uk/FRAX/.
- An appropriate assessment of prevalent fractures and secondary causes of osteoporosis should precede any therapeutic decisions.

Treatment

- The goal of management in osteoporosis is the prevention of fracture. Choice of therapy should be based on a balance of effectiveness, risk and cost.
- Intervention thresholds for therapy can be based on 10-year fracture probability and will be country-specific.
- Alternatively, treatment can be given to all patients with a fragility fracture or a *T*-score of ≤ -2.5 (osteoporosis), or a *T*-score of $< -1.0 > -2.5$ (osteopenia) and additional risk factors, as a large proportion of fractures occur in individuals with osteopenia.
- Monitoring of therapy by serial DXA should be interpreted with caution and take into account the site monitored, time interval, drug-specific expectations and the value of least significant change as calculated for the specific device and operator.
- The monitoring of treatment by biochemical markers of bone turnover is presently not recommended in routine clinical practice.
- The cost-effectiveness of treatments to prevent osteoporotic fracture will be highest where they are used in women who have increased fracture risk. The relevant fracture risk threshold will be specific to the individual health-care system.

Hormonal therapy

- HRT is effective in preventing the bone loss associated with the menopause or secondary amenorrhoea.
- HRT decreases the incidence of all osteoporosis-related fractures, including vertebral and hip fractures, even in populations of women not at high risk of fracture.
- HRT is one of the first-line choices of therapy in postmenopausal women in the age group 50–60 years presenting with a substantial risk of fracture.
- The protective effect of HRT on BMD is lost after cessation of therapy at an unpredictable rate. Although

some degree of fracture protection may remain after cessation of HRT, the patient at high risk for fracture may be a candidate for additional therapy with proven bone-sparing medication.

- The continuation of HRT after the age of 60 years for the sole purpose of the prevention of fractures should take into account the possible side-effects in the individual of the specific dose and method of administration of HRT, compared to other proven therapies.
- The initiation of HRT for the sole purpose of the prevention of fractures is not recommended after the age of 60 years.

Non-hormonal therapy

Calcium and vitamin D

- Postmenopausal women need a dietary reference intake (DRI) of 1000–1200 mg of elemental calcium.
- Calcium supplementation should be restricted to bridge the shortfall between dietary intake and the DRI and to patients being treated for high fracture risk. Routine dietary calcium supplementation cannot be justified in terms of efficacy and health economics. Calcium supplementation in excess of the DRI (total intake) may induce cardiovascular harm.
- The DRI for vitamin D is 800–1000 IU in the postmenopausal period.
- As the major source of vitamin D is dependent on sunlight exposure, the need for supplementation will vary. Measuring the blood 25-hydroxyvitamin D level may be helpful in selected individuals.
- Vitamin D supplementation has been shown independently to lower the risk of fracture and of falling in elderly patients.

Bisphosphonates

- The bisphosphonates are potent inhibitors of bone resorption and decrease the rate of bone turnover, with proven efficacy in the prevention of vertebral and hip fractures.
- A drug-free holiday may be considered after 3–5 years of bisphosphonate therapy in patients with a good BMD response to treatment, without prevalent fractures.
- Bisphosphonates have benefits in some cancers and may prevent bone metastases from breast cancer.
- Bisphosphonate-related osteonecrosis of the jaw is a rare complication when dosages as recommended for fracture prevention are used. An association has been suggested between atypical femur shaft fractures and oversuppression of bone turnover in patients exposed to bisphosphonates for longer than 3–5 years.

SERMs

- The approved SERMs, raloxifene, lasofoxifene and bazedoxifene, reduce the risk of vertebral fracture in postmenopausal women with or without prevalent vertebral fractures. A combination of bazedoxifene and CEE has been shown to preserve BMD.
- Raloxifene is also indicated for reduction in risk of invasive breast cancer in postmenopausal women with osteoporosis, but is associated with an increased risk of venous thromboembolism (VTE) similar to HRT.

Parathyroid hormone

- Parathyroid hormone (PTH) produces a significant reduction in the risk of vertebral and non-vertebral fracture by stimulation of bone formation. There is no indication that combining PTH with a bone resorption inhibitor has any additional benefit to giving either drug alone. Prior treatment with a bisphosphonate blunts the effect of subsequent PTH.
- PTH is given as a daily subcutaneous injection for a maximum of 18 months. Use is limited by high cost.

Strontium ranelate

- Given in a daily oral dose, strontium ranelate significantly reduces the risk of vertebral and non-vertebral fractures in osteoporotic and osteopenic patients, irrespective of the presence of a fracture or age. The mode of action of strontium ranelate involves stimulation of bone formation as well as inhibition of resorption.

Denosumab

- A human monoclonal antibody to the receptor activator of nuclear factor-kappa B ligand (RANKL), at a dose of 60 mg subcutaneously 6-monthly, significantly reduces the risk of vertebral, non-vertebral and hip fractures. As with other biological therapies, denosumab may have adverse immunological effects.

SKIN, CARTILAGE AND OTHER CONNECTIVE TISSUES

Skin, the carotid artery and intervertebral discs

- Estrogen protects connective tissue metabolism in the whole body.
- After the menopause, there is loss of connective tissue in the dermis of the skin which in some cases is reversed with estrogen therapy.

- Similar changes in connective tissue are observed at the arterial media layer.
- Intervertebral discs become thinner after the menopause and this may be prevented by estrogen therapy.

Articulated joints and the menopause

- The marked predominance of polyarticular osteoarthritis in women and, in particular, the marked increase of osteoarthritis in women after the menopause suggest that female sex steroids are important for cartilage homeostasis.
- Timely initiation of estrogen/SERM treatment can effectively prevent both bone and cartilage loss accompanying the menopause, involving both direct and indirect mechanisms.

CARDIOVASCULAR SYSTEM

Gender-specific characteristics of atherosclerosis in menopausal women

- The clinical course of cardiovascular disease has gender-specific characteristics.
- Menopause may be considered a risk factor for coronary artery disease (CAD) in women due to the potential effects of ovarian failure on cardiovascular function, blood pressure and various metabolic parameters (glucose tolerance, lipid profile).
- Arterial hypertension, high triglyceride level and diabetes are more important cardiovascular risk factors in women than in men.
- Preventative strategies should be focused in women on reducing blood pressure and controlling weight and glucose metabolism. Women often have angina with non-obstructed coronary arteries but, when they develop an infarct, their prognosis is significantly worse than that of men.

Postmenopausal hormones and coronary artery disease

- The majority of preclinical data and observational studies support the potential benefits of HRT in reducing risk of CAD. Estrogen may induce beneficial effects on various CAD metabolic risk factors. HRT was found to be associated with a lower risk of new-onset diabetes.
- Randomized controlled trials (RCTs) reported mixed results. RCTs exploring a possible association between cardioprotection and hormone use mainly included women with known CAD or potentially having subclinical atherosclerosis. Those RCTs had insufficient power to assess the effects of hormones on coronary risk in younger symptomatic women initiating therapy around the onset of menopause.
- In both the randomized and observational WHI hormonal trials, although the overall data were not significant for

benefit or harm, over the course of the studies there was a significant trend for decreasing coronary disease with time.

- Patient selection and timing of initiation may explain these apparently conflicting results. Evidence from the major randomized and observational trials points to the importance of age at initiation of hormone use. A coronary benefit has been shown to be confined to women <10 years from the onset of menopause.
- In younger women initiating HRT, all-cause mortality has been shown to be decreased, particularly due to a reduction in cardiovascular disease. Two ongoing prospective trials (KEEPS and ELITE), using carotid intima media thickness and coronary calcium as endpoints, will provide data that may support this benefit.
- Initiation of HRT has been related to more coronary events (termed ‘early harm’) during the first year of use. However, this increased risk appears to be applicable only to elderly women with existing coronary disease and may be related to the estrogen dose at initiation. A difference in the coronary effects of added progestogen compared to estrogen alone has not been established.
- Based on currently available evidence, it is clear that HRT initiation has no place in the routine treatment of older women with coronary disease, and this includes data on raloxifene.

The impact of HRT on stroke

- Although both CAD and stroke are arterial vascular diseases, the effects of postmenopausal hormones on those very common conditions are not necessarily similar.
- Hypertension increases the risk of stroke significantly.
- Oral estrogen therapy and estrogen plus progestogen therapy increase risk of ischemic stroke by about one-third in relatively healthy postmenopausal women. In the WHI study, the excess risk was about one additional stroke per 1000 person-years. Observational findings from the large Nurses’ Health Study are consistent. In another large observational study, transdermal estradiol at a dosage $\leq 50 \mu\text{g}$ did not increase the risk of stroke.
- The excess absolute risk of HRT is expected to be lower among women below the age of 60 years, because stroke incidence is lower in this younger age group. After menopause, the relative risk of stroke does not vary significantly by age or temporal proximity to menopause.
- Evidence from basic science studies reaffirms the neuronal protective effects of estrogen in the setting of experimental infarction.
- Based on findings from a single, well-designed clinical trial of postmenopausal women with a history of ischemic stroke or transient ischemic attack, estrogen therapy should not be prescribed for the secondary prevention of stroke.
- Data on progestogen use versus unopposed estrogen use have not been consistent.

COAGULATION

Venous thromboembolism safety

- VTE is one of the major adverse events during use of oral HRT and SERMs. The risk increases with estrogen dose, age and body mass index and is greater during the first years of therapy.
- Non-oral 17β -estradiol (but not non-oral ethinylestradiol), by avoiding the hepatic first-pass effect, may be preferable for those at increased risk of VTE.
- Population screening for thrombophilia is not indicated prior to HRT use. Selective screening may be indicated on the basis of personal and familial history.

Arterial disease safety

- Oral HRT induces both pro-inflammatory (liver biomarkers) and anti-inflammatory (vascular biomarkers) effects. Modification of inflammation in either direction can be good or bad for arterial disease depending upon the individual status of inflammation in the vascular wall, potentially related to age and time after menopause.
- The liver-derived pro-inflammatory effects of estrogen may be avoided by a non-oral route of administration of 17β -estradiol.
- There is limited evidence that different progestogens modulate liver and vascular inflammatory effects.

BRAIN

General

- During development and adulthood, the human brain is a target for estrogens and other gonadal steroid hormones. Estrogens influence neural function and neurological disease directly, through effects on neurons and glia, and indirectly, through effects on oxidative stress, inflammation, the cerebral vasculature and the immune system.
- With menopause, the cessation of ovarian production of estrogens and progesterone has the potential to influence processes in the central nervous system relevant to neurological and psychiatric disorders. Within the brain, however, some neurons remain capable of synthesizing small amounts of estradiol.
- Many women note cognitive and emotional symptoms at times that are associated with changes in circulating levels of gonadal steroids. It has been more difficult, however, to demonstrate consistent cognitive and affective effects of hormone treatment.

Cognition and cognitive aging

- For midlife women, observational evidence indicates no persisting effects of the natural menopause on memory or

other cognitive functions. During the menopausal transition, however, some women experience transient problems, the magnitude of which is usually small.

- Limited evidence from short-term clinical trials in midlife women suggests that HRT has no substantial cognitive effect after natural menopause.
- For older women without cognitive impairment, there is convincing clinical trial evidence that HRT started in the late postmenopause has no substantial impact on cognitive abilities.
- For surgically menopausal women, limited evidence from small clinical trials suggests that estrogen therapy could be of short-term cognitive benefit when initiated at the time of oophorectomy.
- The long-term cognitive consequences of HRT initiated during the menopausal transition or early postmenopause are unknown. There remains an urgent need for further research in this area.

Alzheimer's disease

- For women with dementia due to Alzheimer's disease, limited clinical trial evidence indicates that HRT does not improve dementia symptoms or slow disease progression.
- Limited clinical trial evidence indicates that HRT increases all-cause dementia risk when initiated in the late postmenopause. For women aged 65–79 years, the excess risk of dementia attributed to hormone use is about 1.2 per 1000 person-years for estrogen therapy and 2.3 per 1000 person-years for estrogen plus progestogen therapy. In this age group, HRT risk may be higher for women with lower cognitive function at baseline.
- Observational evidence implies that HRT used by younger women around the time of menopause is associated with lower risk of Alzheimer's disease. Findings from a recent observational study add new support to the concept of a therapeutic window, suggesting that using HRT in midlife only is beneficial, with respect to dementia risk, whereas starting HRT in later life is harmful. In this study, taking HRT from midlife onward to older age carried a neutral effect on dementia risk.

Depression

- The prevalence of depressive symptoms is similar before and after the menopause. However, depression risk may be increased during the menopausal transition and the early postmenopause.
- Limited clinical trial evidence suggests no effects of estrogen therapy on depression in the late postmenopause.
- Limited clinical trial evidence suggests that short-term estrogen therapy may benefit depression during the menopausal transition.

- There is insufficient evidence to recommend HRT, either alone or as an adjunct, for treatment of depression.

Other neurological disorders

- Potential effects of HRT on the incidence or symptoms of Parkinson's disease are largely unknown.
- Based on evidence from a single, small clinical trial, combined HRT may increase seizure frequency in postmenopausal women with epilepsy.
- Headache prevalence is lower after menopause than before. Observational evidence suggests that current HRT is positively associated with headache.
- Multiple sclerosis symptoms may be influenced by hormonal status. It is not known whether HRT affects multiple sclerosis symptoms or progression.

ONCOLOGY

HRT and breast cancer

- The WHI study demonstrated that 7.1 years of treatment with CEE only did not increase the risk of breast cancer diagnosis in hysterectomized women. The prospective cohort in the Nurses' Health Study also reported that unopposed estrogen did not increase the risk of breast cancer diagnosis until after 15 years of estrogen exposure (mostly CEE). Data about unopposed estradiol are conflicting, with some studies reporting an increased risk of diagnosis with short-term duration, but with others none has been observed.
- Data from the estrogen plus progestogen arm of the WHI showed an increase in breast cancer diagnosis at an average follow-up of 5.6 years, although, after adjustment for confounding variables, this was not statistically significant. Women who had not used HRT prior to the study were not at a higher risk for breast cancer diagnosis for up to 7 years after initiation of therapy.
- Micronized progesterone or dydrogesterone used in association with oral or percutaneous estradiol may be associated with a better risk profile for breast cancer than synthetic progestogens for at least 5 years, but there are not as yet adequately powered clinical studies.
- The risk of breast cancer diagnosis decreases rapidly after cessation of HRT; by 5 years, the risk may not be greater than that in women without any history of exposure.
- Lifestyle factors associated with an increased risk of breast cancer diagnosis include postmenopausal obesity, increased alcohol intake and reduced physical activity.
- Non-modifiable factors include family history, increased breast density and atypical ductal hyperplasia.
- The increased risk of diagnosis observed with HRT may be partially decreased by selecting women with a lower individual baseline risk and by providing education about preventive lifestyle measures. One caveat, however, is that

HRT does not appear to increase the risk of diagnosis in overweight women whereas it does in women who are not overweight. This may be due to differences in circulating estrogen levels related to adiposity.

Endometrial safety, bleeding, HRT and endometrium

- Unopposed estrogen therapy is associated with a duration- and dose-related increase in risk of endometrial hyperplasia and cancer.
- This increased risk persists for many years after cessation of therapy.
- Progestogen prevents the endometrial proliferation of estrogen.
- Endometrial protection requires an adequate dose and duration of progestogen.
- Long-term use of sequential combined HRT regimens may increase the risk of endometrial hyperplasia and cancer, particularly the long-cycle regimens and where progestogens are used for less than 12 days per 30 days.
- Continuous combined regimens are associated with a lower risk of endometrial cancer than in the untreated population.
- In the WHI and Million Women Study, there was no difference in risk of endometrial cancer with continuous combined regimens.
- New lower-dose regimens cause less endometrial stimulation and less bleeding.
- Intrauterine delivery of progestogen is a logical route of administration and provides effective endometrial suppression, but outpatient insertion may be problematic in postmenopausal women.
- Data from RCTs on the effect of tibolone on the endometrium suggest a similar effect to continuous combined regimens.
- Tamoxifen has an estrogenic effect on the endometrium whereas raloxifene and other modern SERMs have no apparent effect.
- Following treatment for endometrial cancer, the use of HRT is not generally recommended, although there are few data.
- Obesity increases the risk of developing endometrial pathology.

HRT and cancers other than breast

Ovarian cancer

- Premenopausal use of the combined oral contraceptive pill is associated with a reduced risk of developing ovarian cancer.
- The WHI study is the only RCT to examine HRT and ovarian cancer risk. In women receiving combined HRT, there was no significant increase in risk.

- Several case-control and population studies suggest a significant increase in risk, but the effect of duration or type of therapy varied among the studies. In one large-scale trial, the increased risk rapidly returned to normal within 2 years of cessation, consistent with a promoter rather than inducer effect.
- In summary, long-term, estrogen-only therapy may be associated with a small attributable risk of ovarian cancer of 0.7 per 1000 women per 5 years of use, whilst either a significantly smaller, or no, increased risk is seen with combined estrogen plus progestogen therapy.

Lung cancer

- Lung cancer incidence in women continues to increase, mainly due to smoking, and lung cancer is the largest contributor to cancer mortality in women.
- Large observational studies have reported a protective effect of hormonal contraception and postmenopausal HRT on lung cancer risk.
- In the WHI RCT of estrogen-only therapy, there was no increase in the risk of non-small cell lung cancer.
- In the WHI RCT of combined estrogen and progestogen therapy, there was an overall non-significant trend towards an increase in risk of non-small cell lung cancer.
- An increased risk became significant only in women aged 60–69 years where the absolute attributable risk was 1.8 extra cases of lung cancer per 1000 women taking HRT for 5 years.
- The risk of death from lung cancer was also higher for HRT users and this increase was greatest amongst those who were smokers.
- In women aged 50–59 years, no increased risk of lung cancer was observed.

Colorectal cancer

- The majority of observational studies show a reduced risk of colorectal cancer amongst users of oral HRT.
- Three meta-analyses have reported a reduced risk of colorectal cancer with HRT use with benefit persisting for 4 years after cessation of therapy. A typical effect was relative risk (RR) 0.80 (95% confidence interval (CI) 0.74–0.86) for ever-users and 0.66 (95% CI 0.59–0.74) for current users.
- Results from the WHI randomized trial of estrogen-only therapy showed no effect of estrogen-only therapy on risk of colorectal cancer.
- In the WHI RCT of estrogen and progestogen therapy, colorectal cancer risk was reduced (RR 0.56; 95% CI 0.38–0.81). This effect was predominantly for local disease and, where spread had occurred, there was more node involvement and a more advanced stage at diagnosis amongst users of HRT.

- HRT should not be used solely for the prevention of colorectal cancer.
- There are no data for an effect of non-oral HRT on risk of colorectal cancer

Cervical cancer

- Long-term cohort studies have shown no increased risk of cervical cancer with HRT use.
- In the WHI RCT, there was no increase in risk of cervical cancer with HRT use.

Upper gastrointestinal tract cancer

- Gastric and esophageal cancers are predominantly diseases of men. The reason for this is unclear and no hormonal mechanism has been found.
- A nested case-control study showed a reduction in stomach cancer for users of HRT (RR 0.48; 95% CI 0.29–0.79) but no effect on esophageal cancer.
- Oral HRT is known to affect gall bladder function and observational studies have reported an increased incidence of cholecystectomy amongst users of HRT.
- The only report of gall bladder cancer and HRT comes from a small case-control study which found an increased risk associated with HRT use and with duration of use (RR 3.2; 95% CI 1.1–9.3).

ATTITUDES TO SEXUALITY AND QUALITY OF LIFE IN THE MENOPAUSE

- Healthy status represents a major determinant of quality of life, particularly in elderly people, but sexuality is an important factor at all ages as well.
- A complex interplay of biological, psychological and socio-relational factors determines women's sexual health. This may negatively affect the entire sexual response cycle, inducing significant changes in desire, arousal, orgasm and satisfaction at menopause and beyond.
- Both age and declining sex hormones have detrimental effects on sexual functioning, with a significant increase in vaginal dryness/dyspareunia and a significant decrease in desire and sexual responsiveness.
- The partner's general and sexual health and the quality of the relationship may significantly contribute to the relevance of sexual symptoms in postmenopausal women.
- Reduced libido is the most common sexual complaint experienced by women and the proportion increases with age. However, there are age-related changes in sexually related personal distress, which are especially evident in surgically menopausal women. These women are at increased risk for hypoactive sexual desire disorder.
- Women may not be willing to initiate a conversation on sexual interest, behavior and activity themselves, but they usually appreciate being questioned by doctors.

- Validated tools (self-administered questionnaires/daily diaries and event logs/semi-structured interviews) may be used to diagnose sexual symptoms and to gain information on sexual constructs and relationships; sex steroid assays are not generally helpful.
- An accurate sexual history and a focused clinical evaluation may help clinicians in the management of sexual symptoms that are causing significant distress. Vaginal atrophy should be always diagnosed and appropriately treated. Hormonal and non-hormonal treatments and/or psychosexual strategies should be individualized and tailored according to a woman's history and current needs.

NEW HORMONAL THERAPIES AND REGIMENS

Newly approved medications and late-stage products

- New low- and ultra-low-dose oral and transdermal preparations appear to maintain benefits for symptom relief and osteoporosis while minimizing side-effects and risks.
- A number of new SERMs have been approved by regulatory agencies for indications related to osteoporosis and a SERM is being evaluated for the treatment of postmenopausal vaginal atrophy.
- Recent IMS recommendations on management of vaginal atrophy have highlighted the excellent benefit/risk ratio of estrogenic and non-hormonal vaginal preparations. An ultra-low-dose vaginal tablet has recently received regulatory approval. Clinical studies are ongoing into the possible use of vaginal dehydroepiandrosterone (DHEA) for atrophy and low libido.
- Studies of SSRI and SNRI products continue to try and find a suitable non-hormonal treatment for hot flushes.
- A SERM/estrogen combination being developed to treat menopausal symptoms and for osteoporosis has completed phase III trials.
- A new injectable monoclonal antibody, targeting RANK ligand, has become available for the prevention of fractures in postmenopausal women with osteoporosis and high fracture risk.
- Transdermal testosterone has been approved in a number of countries for the management of hypoactive sexual desire disorder in surgically menopausal women on concomitant estrogen. Although data exist for use in natural menopause and without concomitant estrogen, these indications have not yet been approved by the regulatory authorities pending further data.

Route of administration

- Non-oral estradiol and progestogens avoid the first-pass metabolism and therefore have the potential for less stimulation of the liver proteins and a neutral metabolic profile.

- The risk of venous thromboembolism is less with transdermal than with oral estradiol.
- First uterine pass of vaginal delivery of progestogens leads to adequate local concentrations and good endometrial protection, but with very low systemic progestogen levels.
- The combination of non-oral administration of estradiol and direct intrauterine delivery of progestogen or vaginal ring delivery of progesterone may improve compliance. Long-term, good-quality studies are still needed.
- Recent observational studies have indicated that the transdermal administration of postmenopausal estrogen is not associated with an increased risk of cardiovascular complications, specifically stroke and venous thrombosis.

Androgen therapy in the postmenopause

- Postmenopausal women with intact ovaries usually do not suffer from androgen deficiency and do not require routine androgen replacement.
- The correlation between women's sexual function and psychosexual variables is complex. Therefore, androgen deficiency can be confounded with other causes of sexual dysfunction such as relationship distress, emotional distress and dyspareunia.
- There is no correlation between serum levels or total androgen activity and sexual dysfunction. Oral methyltestosterone, testosterone undecanoate and transdermal testosterone replacement in oophorectomized as well as in healthy postmenopausal women, with and without concomitant use of estrogens, have shown a beneficial effect in several large RCTs. The administration of a transdermal patch delivering 300 µg of testosterone per day resulted in a significant increase in the number of self-reported sexually satisfying events per month as well as desire, arousal, responsiveness and orgasm, which were impaired at baseline in the participating cohorts.
- Oral DHEA does not significantly improve sexual function except in women suffering from adrenal insufficiency. There are no data on breast and endometrial safety with DHEA use.
- The role of vaginal DHEA administration for improving sexual function in postmenopausal women is controversial.

NON-HORMONAL APPROACHES TO THE MANAGEMENT OF MENOPAUSAL SYMPTOMS

Non-pharmacological and lifestyle interventions

- High-quality data from studies of non-pharmacological and lifestyle interventions for vasomotor symptoms have been limited.
- Meditation, relaxation, controlled breathing and cognitive behavior therapy show promise in managing hot flushes, but adequately powered randomized trials are still needed.

- There is little evidence that dietary modifications or exercise improve hot flushes but they may improve mood and quality of life. Regular exercise, weight reduction, and avoiding triggers to hot flushes (such as caffeine or direct heat) may help to minimize hot flushes or their impact.
- Randomized trials of acupuncture have not consistently shown a beneficial effect in reducing vasomotor symptoms.

Complementary therapies for vasomotor symptoms

- High-quality studies to date have not consistently supported the efficacy of complementary or over-the-counter therapies in reducing severity or frequency of hot flushes or night sweats.
- Black cohosh and soy products are not superior to placebo in the treatment of hot flushes.

So-called 'bioidentical' or 'natural' hormones

- Such labelling and advertising has no sound scientific basis to delineate them from many current forms of registered HRT.
- Estradiol, estrone or estriol, whether pharmaceutically produced or compounded as a 'bioidentical' product, are synthesized usually from the vegetable yam and are identical to ovarian estrogens.
- Other so-called 'natural' but synthesized human hormones that can be mixed into untested 'bioidentical' concoctions can be progesterone, testosterone, DHEA, thyroxine, growth hormone and melatonin.
- These hormones are usually administered in troches (buccal lozenges) or transdermal creams, compounded by local chemists on the prescription of medical practitioners, in combinations and doses that have never been tested in published quality clinical trials.
- There are inadequate quality data to show the long-term safety or efficacy of any of these products.
- Endometrial cancer has been associated with estrogen-containing bioidentical hormones. If used in the bioidentical mixture at all, the progesterone used may not inhibit estrogen-induced endometrial hyperplasia.
- Hormonal assay of saliva is sometimes claimed as a way of assessing hormonal need and of titrating the compounded 'natural' hormones. There are no data to show that salivary hormonal assay can reliably achieve these aims.
- Bioidentical hormones are extensively marketed direct to the public on the internet and in other media, often with unproven and unlikely claims such as they have no side-effects, are safe, will help you lose weight and are anti-aging.
- Locally compounded 'bioidentical' hormones are not subject to the scrutiny of pharmaceutical regulatory bodies in many countries and the manufacturers can avoid having to test their products for quality control, safety and efficacy.

- These unproven products and the associated inaccurate saliva tests are usually promoted for commercial gain and are much more expensive than proven registered pharmaceutical hormone therapies.
- All main-stream scientific, clinical and regulatory bodies in women's health advise against the prescription and use of these hormones.
- The prescriber is at risk of future medicolegal claims.

Pharmacological agents for vasomotor symptoms

- The mechanisms underlying vasomotor symptoms are still not well understood.
- There have been very few head-to-head studies of non-hormonal agents.
- Currently, the only preparation which has demonstrated equivalent efficacy to estrogen is gabapentin. Gabapentin (300 mg three times per day) was equivalent to low-dose estrogen (0.5 mg CEE or a 25 µg estradiol patch) for vasomotor symptoms.
- No other agents have been directly compared with estrogen for the reduction of vasomotor symptoms.
- Venlafaxine, desvenlafaxine, fluoxetine, paroxetine and citalopram have all been shown in RCTs to reduce vasomotor symptoms. A recent head-to-head study found that venlafaxine (37.5 mg per day increasing to 75 mg controlled release) was equally effective but better tolerated than gabapentin (300 mg once per day increasing to 300 mg three times per day) in breast cancer patients. Both products reduced the frequency and severity of hot flushes (by 66%) but side-effects were greater with gabapentin.
- In breast cancer patients, the SNRI venlafaxine was equally as effective as clonidine in reducing vasomotor symptoms but clonidine was better tolerated. Efficacy up to 12 weeks has been demonstrated for these agents.
- In general, these non-hormonal agents reduce hot flushes by 50–60%. This level of reduction appears to be acceptable to many women who wish to avoid hormones.
- For those with mild/moderate hot flushes, it is reasonable to start with clonidine treatment. For moderate to severe hot flushes, or when clonidine fails or is not available, consider venlafaxine or gabapentin. These agents may act by different mechanisms, so, if one fails or is not well tolerated, the other can be tried. If these are not effective, consider paroxetine, but avoid in those on tamoxifen.
- A key consideration in breast cancer patients using non-hormonal agents is concomitant tamoxifen use. Agents which inhibit the enzyme CYP2D6 can affect tamoxifen metabolism and may reduce the efficacy of tamoxifen in preventing new breast cancers or their recurrence. Agents which interact with the cytochrome P450 system include paroxetine, fluoxetine and bupropion and these should not be used in conjunction with tamoxifen for the treatment of depression or vasomotor symptoms. For use

with tamoxifen, venlafaxine, desvenlafaxine, citalopram and escitalopram appear to be safe.

- Sudden cessation of a SNRI or SSRI may cause withdrawal symptoms and they should be discontinued gradually by reducing the dose over 2 weeks.

POSTMENOPAUSAL VAGINAL ATROPHY

- Vaginal atrophy becomes clinically apparent 4–5 years after the menopause and objective changes as well as subjective complaints are present in 25–50% of all postmenopausal women.
- It is essential that health-care attendants routinely engage in open and sensitive discussion with postmenopausal women about their urogenital health to ensure that symptomatic atrophy is detected early and managed appropriately.
- Treatment should be started early and before irrevocable atrophic changes have occurred.
- Treatment needs to be continued to maintain the benefits.
- All local estrogen preparations are effective and patient preference will usually determine the treatment used.
- All currently available topical estrogens are absorbed, the extent depending on dose and formulation.
- Additional progestogen is not indicated when appropriate low-dose, local estrogen is used although long-term data (more than 1 year) are lacking.
- If estrogen is ineffective or undesired, vaginal lubricants and moisturizers can relieve symptoms due to dryness.
- There are few data on the use of vaginal estrogens in women with gynecological hormone-responsive cancers so they should be used with discretion.
- Use of local estrogen in women on tamoxifen or aromatase inhibitors needs careful counselling and discussion with the patient and the oncology team.

INFLUENCE OF METHODOLOGY AND EPIDEMIOLOGY ON PERCEPTION OF HRT

- There is a hierarchy of scientific evidence which should be taken into account when drawing conclusions from any scientific investigation. In general (from the highest standard or level of evidence to the lowest), the standards of evidence are: meta-analyses of RCTs, RCTs, observational trials, and, lastly, expert opinion. However, both RCTs and observational trials must be interpreted with caution, particularly in reference to HRT.
- Observational trials (e.g. the Nurses' Health Study) are primarily used for hypothesis development and not to prove cause and effect. Inherent biases in observational studies of HRT typically include: selection bias – healthier women prescribed HRT; prevention bias – monitoring and treatment more intensive in women prescribed HRT; compliance bias – patients with greater adherence (even to placebo) have better outcomes; survivor bias – HRT may be stopped due to illness; prevalence-incidence

bias – early adverse effects of HRT not observed if user dies before becoming part of cohort.

- RCTs (e.g. WHI) are primarily used for hypothesis testing, to prove or disprove cause and effect. They can be downgraded in their level of evidence due to mitigating factors such as: a large dropout rate, lack of adequate representation of the applicable group of women, and the modifying influence from prior hormone use, for example. The WHI was recently downgraded to a level of evidence equal to an observational trial.
- The World Health Organization (WHO) Council for International Organizations of Medical Sciences (CIOMS) classifies the frequency of drug reactions, which would include the impact of HRT or estrogen therapy, as:

Very common > 1/10 (>10%)

Common (frequent) >1/100 and <1/10 (>1% and <10%)

Uncommon (infrequent) >1/1000 and <1/100 (>0.1% and <1%)

Rare >1/10 000 and <1/1000 (0.01% and <0.1%)

Very rare <1/10 000 (<0.01%)

However, these frequencies do *not* necessarily indicate clinical relevance. Rare findings in very large RCTs and observational trials may be statistically significant because of the large sample size, but may be clinically irrelevant in their application to a particular patient in the clinical setting. Failure to provide a clinical context is often a significant problem in relation to study outcomes. This is one of the reasons for providing the absolute risks noted above. In one study, for example, electric blanket use was associated with a relative risk equal to 5 for breast cancer.

INFLUENCE OF THE MEDIA ON PERCEPTION OF HRT

- The mass media has a tremendous influence over what the public ‘knows’ about HRT. Media-driven perceptions also influence clinical decision-making, particularly by those less familiar with the primary data being reported by the media. Each new news report is treated as if it were the most important and of the highest quality, often to the exclusion of the bulk of scientific evidence. For example, the initial results of the WHI estrogen plus progestogen arm received enormous media coverage – more than 400 newspaper stories and 2500 television-radio stories in the US alone, yet subsequent WHI reports have received much less press coverage, leading to the impression that surgically menopausal women on estrogen without progestogen have similar risks as noted in the initial reports (WHI estrogen plus progestogen arm).
- The press tends to focus on negative news (e.g. breast cancer) to the exclusion of any positive findings such as all-cause mortality, cardiovascular disease prevention in younger women, or fracture reduction. Also, media

coverage sometimes includes totally wrong reports, or superficial and uncritical evaluations taken from the abstracts of selected journals, without reference to the entire article or the author’s own discussion of the findings.

- Media coverage has done a good job of telling women what to be concerned about if they are using HRT, but a poor job of providing the information women need to determine whether the latest findings apply to them.
- There is a general distrust of large organizations and particularly of research done by the pharmaceutical industry, despite its conformance to regulatory agencies, both in the US (FDA) and in other countries of the world (e.g. EMEA). This distrust leads to denial of the findings if they do not agree with one’s own preconceived expectations. Even when the findings are unexpectedly positive, they are often assumed to be spurious or falsified in the name of profit.

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