IMS Updated Recommendations on postmenopausal hormone therapy

Issued on behalf of the Board of the International Menopause Society by Amos Pines (President), David W. Sturdee (General Secretary), Martin H. Birkhäuser (Treasurer), Hermann P. G. Schneider, Marco Gambacciani and Nick Panay

INTRODUCTION

The past decade has seen marked fluctuations in opinions concerning the merits and risks of postmenopausal hormone therapy. In July 2002, menopause management faced a major turning point when the first data from the Women’s Health Initiative (WHI) trial were released. The study was categorized as a primary prevention trial for coronary heart disease, although the fact that mean age at recruitment was 63 years was not given enough importance at that time. WHI investigators concluded that hormone therapy (HT) was not cardioprotective, and, in fact, 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 HT 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 the IMS Workshop held in Vienna (December 2003) and the IMS Position Paper that was based on the Workshop discussions. Looking at global perspectives, and being independent of local or regional constraints imposed by official health authorities, this IMS Statement called for a more balanced approach in the interpretation of the scientific data on hormone use that were available in 2003. Since then, additional information has been accumulated from both arms of the WHI study, observational trials and from other studies, allowing a more comprehensive review on all issues related to the use of hormones in the postmenopausal period. In view of the above, the IMS Board decided that it is time to update the 2004 Statement and to enlarge its scope to menopause management and adult women’s health in general. More than 30 experts from the various fields of menopause medicine reviewed the latest information in a Workshop held in Budapest in February 2007.

The following Recommendations express the views of the IMS on the principles of hormone therapy in the peri- and postmenopausal periods. Throughout the Recommendations, the term HT will be used to cover all therapies including estrogens, progestogens, combined therapies and tibolone.

The previous IMS Statement in 2004 is still valid and serves as a basis for the current Updated Recommendations.

We are 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, which may all impact on hormone therapy. The following recommendations, therefore, give a global and simple overview that serves as a common platform on issues related to the various aspects of hormone treatment. These Recommendations were reviewed and discussed by representatives of more than 60 National and Regional Menopause Societies from all continents. These Recommendations can be easily adapted and modified according to local needs.

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GOVERNING PRINCIPLES

Hormone therapy should be part of an overall strategy including lifestyle recommendations regarding diet, exercise, smoking and alcohol for maintaining the health of postmenopausal women. HT 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 HT differ for women around the time of menopause compared to those for older women.

HT 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.

Women experiencing a spontaneous or iatrogenic menopause before the age of 45 years and particularly before 40 are at higher risk for cardiovascular disease and osteoporosis. They will benefit from hormone replacement, which should be given at least until the normal age of menopause.

Counselling should convey the benefits and risks of HT in simple terms, e.g. absolute numbers rather than as percentage changes from baseline expressed as a relative risk. This allows a woman and her physician to make a well-informed decision about HT.

HT should not be recommended without a clear indication for its use.

Women taking HT should have at least an annual consultation to include a physical examination, update of medical history, relevant laboratory and imaging investigations and a discussion on lifestyle.

There are no reasons to place mandatory limitations on the length of treatment.

Whether or not to continue therapy should be decided at the discretion of the well-informed hormone user and her health professional, dependent upon the specific goals and an objective estimation of benefits and risks.

Dosage should be titrated to the lowest effective dose. Lower doses of HT than have been used routinely can maintain quality of life in a large proportion of users. Long-term data on lower doses regarding fracture risk 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. Low-dose vaginal estrogens administered for the relief of urogenital atrophy do not require progestogen co-medication. Direct delivery of progestogen to the endometrial cavity from the vagina or by an intrauterine system is logical and may minimize systemic effects.

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

BENEFITS OF HORMONE THERAPY

General

HT remains the most effective therapy for vaso-motor and estrogen-deficient urogenital symptoms. Other menopause-related complaints, such as joint and muscle pains, mood swings, sleep disturbances and sexual dysfunction (including reduced libido) may improve during HT. Quality of life and sexuality are key factors to be considered in the management of the aging individual. The administration of individualized HT (including androgenic preparations when appropriate) improves both sexuality and overall quality of life.

Postmenopausal osteoporosis

HT is effective in preventing the bone loss associated with the menopause and decreases the incidence of all osteoporosis-related fractures, including vertebral and hip, even in patients at low risk. Although the magnitude of decline in bone turnover correlates with estrogen dosage, even lower than standard-dose preparations maintain a positive influence on bone indices in most women. Based on updated evidence on effectiveness, cost and safety, HT is an appropriate first-line therapy in postmenopausal women presenting with an increased risk for fracture, particularly under the age of 60 years and for the prevention of bone loss in women with premature menopause. The protective effect of HT on bone mineral density declines after cessation of therapy at an unpredictable rate, although some degree of fracture protection may remain after cessation of HT.

The initiation of standard-dose HT is not recommended for the sole purpose of the prevention of fractures after the age of 60 years. Continuation of HT 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 HT, compared to other proven therapies.

**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, and diabetes and lipid control. There is evidence that HT may be cardioprotective if started around the time of menopause and continued long-term (often referred to as the 'window of opportunity' concept). HT markedly reduces the risk of diabetes and, through improved insulin resistance, it has positive effects on other risk factors for cardiovascular disease such as the lipid profile and metabolic syndrome.

In women less than 60 years old, recently menopausal and without prevalent cardiovascular disease, the initiation of HT does not cause early harm and in fact reduces cardiovascular morbidity and mortality. Continuation of HT beyond the age of 60 should be decided as a part of the overall risk–benefit analysis.

**Other benefits**

HT has benefits for connective tissue, skin, joints and intervertebral disks. HT may reduce the risk of colon cancer. HT initiated around the time of menopause or by younger postmenopausal women is associated with a reduced risk of Alzheimer’s disease.

**POTENTIAL SERIOUS ADVERSE EFFECTS OF HORMONE THERAPY**

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 cannot necessarily be generalized. The degree of association between breast cancer and postmenopausal HT remains controversial.

Women should be reassured that the possible risk of breast cancer associated with HT is small (less than 0.1% per annum). For combined HT, observational data from the Million Women Study suggested that breast cancer risk was increased as early as the first year, raising serious reservations on possible methodologic flaws. On the contrary, randomized controlled data from the Women’s Health Initiative (WHI) study indicate that no increased risk is observed in women initiating HT, for up to 7 years. It should be noted that the majority of subjects in the WHI study were overweight or obese.

Data from the WHI and 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 American women. Recent European observational studies suggest that risk may increase after 5 years.

There are insufficient data to evaluate the possible differences in the incidence of breast cancer using different types and routes of estrogen, natural progesterone and progestogens, and androgen administration.

Baseline mammographic density correlates with breast cancer risk. This does not necessarily apply to the increase in mammographic density induced by HT.

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.

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.

**Thromboembolism and cardiovascular events**

The HT-related risk for serious venous thromboembolic events increases with age (although minimal until age 60), and is also positively associated with obesity and thrombophilia. By avoiding first-pass hepatic metabolism, transdermal estrogen may avert the risk associated with oral HT. The impact on the risk of a thromboembolic
event may also be affected by progestogen, depending on the type. Late starters of standard-dose HT may have a transient slightly increased risk for coronary events. The risk of stroke is correlated with age. HT may increase the risk of stroke after the age of 60.

Safety data from studies of low-dose and ultralow-dose regimens of estrogen and progestogen are encouraging.

ALTERNATIVE TREATMENTS

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

Selective serotonin reuptake inhibitors, selective noradrenaline reuptake inhibitors 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 tested in studies and their purity and risks are unknown.

RESEARCH

There is urgent need for further research especially into the relative merits of lower doses, regimens and routes of administration.

CONCLUSION

The safety of HT largely depends on age. Women younger than 60 years old should not be concerned about the safety profile of HT. New data and reanalyses of older studies by women's age show that, for most women, the potential benefits of hormone therapy given for a clear indication are many and the risks are few when initiated within a few years of menopause. In view of the new data, Regulatory Authorities should review their current recommendations as a priority.

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APPENDIX: Key messages from the lectures, abstracted by the speakers, on adult women's health presented at the IMS Budapest Workshop, February 2007

HEALTHY LIFESTYLE

Exercise in the menopause – an update

- Any physical activity is better than being sedentary.
- Regular exercise reduces total and cardiovascular mortality.
- Better metabolic profile, balance, muscle strength, cognition and quality of life are observed in physically active persons. Heart events, stroke, fractures and breast cancer are significantly less frequent.
- Benefits far outweigh possible adverse consequences: the more, the better, but too much may cause harm. Injury to the musculoskeletal system should be avoided.
- Optimal exercise prescription is at least 30 minutes of moderate-intensity exercise, at least three times weekly. Two additional weekly sessions of resistance exercise may provide further benefit.

Healthy lifestyle

- Obesity (body mass index >30 kg/m²) affects over 20% of the population 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: four to five servings/day of fruits and vegetables, whole grain fibers, fish twice a 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 own health.

**UROGYNECOLOGY**

- Symptoms such as vaginal dryness, soreness, dyspareunia, urinary frequency and urgency are extremely common in postmenopausal women. Incontinence in women seems to increase with age, from 3–5% at age 20, 8–9% at age 30 and 12–15% at age 50.

- However, there is a huge inter-individual as well as intra-individual sensitivity to these changes, and symptoms and signs of urogenital aging are therefore highly variable within an individual as well as between individuals.

- The loss of lubrication and glandular functions severely impairs sexual desire. 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 hormone therapy does not seem to prevent urinary incontinence.

- Antimuscarinic drugs combined with local estrogens constitute first-line treatment in women with urge incontinence and/or overactive bladder.

- Surgery remains the prime option for perimenopausal women with pure stress incontinence in whom hormone therapy may even worsen the situation.

**OSTEOPOROSIS**

**Hormonal therapy (HT)**

- HT is effective in preventing the bone loss associated with the menopause.

- HT decreases the incidence of all osteoporosis-related fractures, including vertebral and hip fractures, even in patients at low risk for fractures.

- HT is indicated for the prevention of bone loss in women with premature menopause and secondary amenorrhea.

- HT is indicated in postmenopausal women in the age group 50–60 years presenting with a risk for fracture.

- Potential adverse effects of HT can be limited by using lower than standard doses or by avoiding oral administration, without compromising the beneficial effect of HT on bone.

- The protective effect of HT on bone mineral density is lost after cessation of therapy at an unpredictable rate. Although some degree of fracture protection may remain after cessation of HT, the patient at risk for fracture should receive additional therapy with proven bone-sparing medication.

- The continuation of HT after the age of 60 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 HT, compared to other proven therapies.

- The initiation of HT 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**: Some studies suggest that the combination of calcium and vitamin D is able to reduce the risk of falling, and decreases the hip fracture risk, provided the dose of vitamin D is more than 700 IU per day. Other data suggest that the efficacy of the combined calcium and vitamin D regimen primarily relies on the component calcium.

- **Bisphosphonates**: With bisphosphonates, bone turnover normalizes within weeks and no further suppression is seen during long-term use with up to 10 years of continuous administration. Both vertebral and non-vertebral antifracture efficacies are detectable after 6 months of treatment. The antifracture efficacy seems to last more than 5 years after cessation of treatment.

- **SERMs**: The selective estrogen receptor modulator (SERM) raloxifene reduces the risk of vertebral fracture in postmenopausal women with or without prevalent vertebral fracture. New SERMs and a SERM/HT combination are in final stages of development.

- **Parathyroid hormone (PTH)** produces a significant reduction in the risk of vertebral and non-vertebral fracture. There is no indication that combining PTH with a bone resorption inhibitor has any additional benefit to giving either drug alone.

- **Strontium ranelate** is a new agent for the treatment of osteoporosis, combining mild decreased bone resorption and maintained bone formation. It significantly decreases the
risk of new vertebral fracture and also reduces the relative risk of non-vertebral fractures.
* New therapeutic possibilities such as the humanized monoclonal antibody to the receptor activator of nuclear factor-kappa B (RANK) ligand (RANKL) denosumab are under investigation. First results are promising.

Guidelines on osteoporosis
* Optimal skeletal health is dependent on an appropriate lifelong balance of calcium/vitamin D nutrition and exercise.
* Bone mineral density (BMD) assessment by DXA is the basis for the diagnosis of osteoporosis.
* The various bone assessment techniques, including DXA, ultrasound and computed tomography, offer complementary tools for the assessment of fracture risk, but the most important single measure is total hip DXA.
* Site-specific assessments provide the best guide to future fracture risk at that site.
* A large proportion of fractures occur in individuals who do not have BMD-defined osteoporosis.
* BMD is not a cost-effective population screening tool but is best applied on a selective basis, based on age and other risk factors, some of which have an influence on fracture risk that is independent of BMD.
* The goal of management in osteoporosis is the prevention of fracture.
* Ten-year fracture probability is the most useful estimate for therapeutic intervention.
* Individual fracture probability should be based on the combination of bone mineral density, age and other clinical risk factors.
* 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.
* Choice of therapy should be based on a balance of effectiveness, risk and cost.

SKIN, CARTILAGE AND OTHER CONNECTIVE TISSUES
Skin, the carotid artery and intervertebral discs
* Menopause inflicts a negative effect on the connective tissue in the dermis of the skin. Such an effect is prevented and in some cases reversed with estrogen therapy.
* Similar changes in connective tissue are observed at the arterial media layer.
* Apart from its positive effect on the bone, it was recently found that estrogen induces favorable changes at the intervertebral discs. The menopause, on the other hand, has a negative effect on discs, just like in bone.
* Estrogen deprivation, on the one hand, and estrogen therapy, on the other, probably leads to changes in the connective tissue matrix at many other sites and organs in addition to the aforementioned tissues.

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 both point to a likely involvement of female sex steroids in the maintenance of cartilage homeostasis.
* In postmenopausal women treated with levormeloxifene, the urinary excretion of C-telopeptide of type II (CTX-II), a biomarker for cartilage turnover, is decreased by approximately 50%. CTX-II levels are restored to the premenopausal range. Bone resorption is similarly restored to premenopausal levels.
* Timely initiated estrogen/SERM treatment can effectively prevent both bone and cartilage loss accompanying the menopause, involving both direct and indirect mechanisms.

CARDIOVASCULAR PROBLEMS
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 in women due to the potential effects of ovarian senescence on cardiac function, blood pressure and various metabolic parameters (glucose tolerance, lipid profile).
* Arterial hypertension 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 normal 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 HT benefits in reducing risk of coronary artery disease (CAD).
- Randomized controlled trials (RCTs) reported mixed results. RCTs exploring 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 at 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 point 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.
- Initiation of hormone therapy 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 prevalent coronary disease.
- Emerging data strongly suggest a possible coronary benefit in younger healthy women who also do not experience early harm. These suggestions remain to be confirmed in prospective trials.
- Whether there is a difference in the coronary effects of added progestogen compared to estrogen alone has not been established, but effects may be more favorable with the use of estrogen alone.
- Based on currently available evidence, it is clear that hormonal therapy has no place in the treatment of older women with coronary disease, and this includes recent data on raloxifene.

Menopause and stroke: special features and impact of HT

- Although both CAD and stroke are arterial vascular diseases, the effects of postmenopausal hormones on those very common conditions are not necessarily similar.
- Hormone therapy has been listed as a risk factor for stroke, although the data in menopausal women are not consistent. The existence of hypertension was shown to significantly increase the risk.
- The increased risk for ischemic stroke in the WHI population was in the order of 1 additional case/1000 women-years, which makes it by definition a rare event. However, the risk was not increased in the 50-59-year-old age group, which is in keeping with data from recent observational trials in younger, normotensive cohorts.
- Subanalyses of observational cohorts suggested the risk to be less with lower doses of estrogen, particularly when lower doses are prescribed soon after menopause. In addition, the risk is possibly even lower with non-oral therapy.
- There is a body of evidence from basic science studies which reaffirms the neuronal and stroke-protective effects of estrogen. Thus, the discrepancy between these data and clinical data showing no benefit or increased risk of stroke remains to be explained.
- Data on progestogen use versus unopposed estrogen use have not been consistent.

COAGULATION

Venous thromboembolism safety

- Venous thromboembolism (VTE) is one of the major adverse events during HT. The risk increases with age and body mass index, but is also particularly increased during the first years of therapy.
- Oral estrogens reduce fibrinolysis.
- Non-oral estrogens, by avoiding the hepatic first-pass effect, have minimal effect on coagulation, and may be preferable for those at increased risk of VTE.
- Specific progestogens are capable of reducing the impact of oral estrogens on anticoagulant factors.
- Population screening for thrombophilia is not indicated. Selective screening can be indicated on the basis of personal and familial history.

Arterial disease safety

- HT 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.

- The liver-derived pro-inflammatory effects of estrogen may be avoided by a non-oral route of administration. Using low doses of oral estrogen potentially decreases these changes, but the dose-response curve is close to the dose-response curve for efficacy.
- Limitation of vascular anti-inflammatory effects is a target not yet achieved. Both oral and non-oral HT exhibit vascular-derived anti-inflammatory actions, although possibly with different magnitude.
- There is limited evidence that different progestogens modulate liver and vascular inflammatory effects.

CENTRAL NERVOUS SYSTEM/PSYCHIATRY

Cognition and cognitive aging

- For younger women, observational evidence suggests no substantial cognitive sequelae from the natural menopausal transition; limited evidence from clinical trials suggests that HT has no substantial cognitive effect after natural menopause, at least in the short term.
- For younger women, there is limited evidence from clinical trials that estrogen therapy may be of short-term cognitive benefit in the setting of surgical menopause.
- For older women, HT started in the late postmenopause probably does not have a substantial impact on cognitive abilities.
- The long-term cognitive consequences of HT initiated during the menopausal transition or early postmenopause are unknown. The need for further research in this area is urgent.

Alzheimer’s disease and other neurological disorders

- During development and adulthood, the human brain is a target for estrogen and other steroid hormones. Estrogen influences neural function and neurological disease directly, through effects on neurons and glia, and indirectly, through effects on the cerebral vasculature and immune system.

- With menopause, the cessation of ovarian estrogen production and the initiation of HT have the potential to influence processes in the central nervous system relevant to a variety of neurological disorders.
- For women with Alzheimer's disease (AD), limited evidence from clinical trials indicates that HT does not improve symptoms or slow disease progression.
- There is limited evidence from clinical trials that HT increases dementia risk when initiated after the age of 64.
- Observational evidence implies that HT used by younger women around the time of menopause is associated with lower risk of AD. However, findings may be biased, and further research is needed to determine whether there might exist an early window during which the effects of HT on AD risk are beneficial rather than harmful.
- Potential effects of HT on the incidence or symptoms of Parkinson's disease are largely unknown.
- Based on evidence from a single clinical trial, combined HT may increase seizure frequency in postmenopausal women with epilepsy.

Estrogen: effects on normal brain function, and neuropsychiatric disorders

- Many women complain of memory and other cognitive/emotional difficulties at times that are associated with changes in estrogen levels.
- However, the biological mechanisms through which estrogen may exert these effects remain poorly understood. Also, the effect of estrogen treatment on cognition and brain function in healthy women and those with Alzheimer's disease is controversial.
- There is evidence that, in healthy women, estrogen affects the dopaminergic, serotonergic and cholinergic systems, and brain regions crucial to higher cognitive function and mood.
- New results from recent in vivo randomized, controlled neuroimaging experiments demonstrate that, in young females and those in mid-life:
  - brain function is modulated by normal variation in ovarian function;
  - acute loss of ovarian hormones increases neuronal membrane breakdown;
  - acute suppression of ovarian function is associated with reduced activation of brain regions critical to memory.
ONCOLOGY

Breast cancer prevention

- The lobular breast attains its maximum development during pregnancy and lactation (Lob. 4). After menopause, mammary lobules in both nulliparous and parous women regress to structures designated Lob. 1.
- Undifferentiated lobules (Lob. 1) in the breast of nulliparous women retain a high concentration of epithelial cells (Stem cells 1) that are targets for carcinogens and therefore susceptible to undergo neoplastic transformation.
- Early first full-term pregnancy imprints in the breast epithelial cells a genomic signature (Stem cells 2), making them refractory to transformation.
- The Stem cell 2 contains specific genes controlling transcription, RNA processing, immune response, apoptosis, DNA repair and DNA recombination. Their coded proteins may serve as biomarkers for breast cancer protection.
- Clinical studies are under way to induce in the human breast a genomic signature of Stem cell 2 and thereby confer cancer protection. This concept may pave the way to long-term oncological prevention.

Hormone therapy and breast cancer

- Estrogen associated with breast cancer development is not circulating estrogen but rather that produced locally within the breast.
- Excessive formation of catechol estrogen quinones initiates a series of events leading to breast cancer, by reacting with DNA. Endogenous estrogen is detrimental primarily in those women with genetic susceptibility.
- The WHI study demonstrated that 7.1 years of treatment with estrogen only did not increase the risk of breast cancer in hysterectomized women. The prospective cohort in the Nurses’ Health Study also reported that unopposed estrogen did not increase the risk of breast cancer until after 15 years of estrogen exposure.
- Data from the estrogen plus progestogen arm of the WHI showed an increase in breast cancer risk at an average follow-up of 5.6 years. However, women who had not used HT prior to the study were not at a higher risk for breast cancer 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 no increase in risk or lower risk than use of synthetic progestogens for at least 4 years, and perhaps even 8 years, of treatment.
- The risk of breast cancer decreases rapidly after cessation of HT; by 5 years, the risk may not be greater than that in women without any history of exposure.

Endometrial safety, bleeding, hormone therapy and endometrium

- Progestogen prevents the endometrial proliferation of estrogen.
- Continuous combined regimens are associated with a lower risk of endometrial cancer than in the untreated population.
- New lower-dose regimens cause less endometrial stimulation and less bleeding.
- Intrauterine delivery of progestogen is a suitable and logical route of administration.
- The protective effect of progestogen on the endometrium has to be balanced against the apparent adverse effect on breast cancer risk.
- Data on the effect of tibolone on the endometrium from randomized, controlled trials suggest a similar effect to continuous combined regimens.

NEW ATTITUDES TO SEXUALITY AND QUALITY OF LIFE IN THE MENOPAUSE

Clinical evaluation/diagnosis

- 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.
- Desire difficulty is the most common sexual complaint experienced by women and the proportion of women with low desire 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 properly to diagnose sexual symptoms and to gain information on sexual constructs and relationships, while hormonal assays are presently not considered a standard of routine practice.
• An accurate sexual history and a focused clinical evaluation may help clinicians in the management of sexual symptoms that are causing significant distress. Hormonal and non-hormonal treatments, and/or psychosexual strategies should be individualized and tailored according to a woman's history and current needs.

Menopause and aging, quality of life and sexuality
• 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.
• Sexuality is less often a problem for women than for men.
• Hormonal changes which are associated with aging or menopause may deeply affect quality of life.
• Therapeutic interventions such as hormonal or non-hormonal treatments, targeting selected diseases or components of the aging process, may improve quality of life and sexuality in both sexes.

NEW HORMONAL THERAPIES AND REGIMENS

Regulatory authorities’ statements
• Regulatory Authorities are constituted in the interests of Public Health and not the individual patient.
• The composition of the committees is of paramount importance in determining outcome.
• Publications since 2003 have not impacted much on either Recommendations or information published.
• Further review by an independent organization is to be recommended.

New products and regimens since 2003
• New products are being developed which maintain benefits and minimize risks. However, some useful products have been withdrawn by pharma companies through profitability decisions.
• New ultra-low-dose oral preparations appear to maintain benefits for symptom relief and osteoporosis whilst minimizing side-effects and risks.
• New progestogens can minimize progestogenic side-effects through anti-androgenic and anti-mineralocorticoid effects, e.g. drospirenone.
• Endometrial protection may not be needed with the ultra-low-dose transdermal system (14 μg/day).
• A new female androgen patch will be licensed for treatment of female androgen deficiency causing distress (hypoactive sexual desire disorder).
• A non-hormonal option, selective noradrenaline reuptake inhibitor, for vasomotor symptom management is currently in development in phase III clinical trials.
• A SERM/estrogen therapy combination is in phase III clinical trials and showing encouraging data for efficacy/risks.

Route of administration and timing of initiation
• Non-oral estradiol and progestogens circumvent the first-pass metabolism and therefore have the potential for a lesser stimulation of the liver proteins and a relevant neutral metabolic profile, which might be more favorable in terms of cardiovascular and venous thromboembolism risk.
• The risk of venous thromboembolism has been shown to differ significantly when transdermal estradiol was compared with oral estradiol. However, whether this is related to a differential impact of estradiol on clotting factors synthesized in the liver has not been confirmed.
• It is assumed that lower circulating levels of progestogens will have less negative impact on breast cancer risk, if any.
• First uterine pass of vaginal delivery of progestogens leads to adequate local concentrations and good endometrial protection, but with very low systemic progestogen levels.
• Combination of non-oral administration of estradiol and direct intrauterine delivery
of progestogen may improve compliance and minimize the risks of hormone replacement. However, long-term, good-quality studies to confirm this hypothesis are still needed.

- Further analysis of randomized, controlled and prospective studies indicates that early administration of hormone therapy in younger postmenopausal women can afford protection against cardiovascular disease, while initiation of therapy at an older age, after 10 years without endogenous estrogen, is harmful.

**Androgens**

- Androgen production is usually preserved in the menopause, and therefore, postmenopausal women usually do not suffer from androgen deficiency and do not require routine androgen replacement.
- The definition of female androgen deficiency is not precise enough and may lead to over-diagnosis.
- Androgen replacement in healthy postmenopausal women has shown no beneficial effect in published trials and currently cannot be recommended.
- Androgen replacement should be reserved for women with severe androgen deficiency due to an established cause and matching clinical signs and symptoms.
- Randomized, controlled trials on androgen replacement in women with bilateral oophorectomy or adrenal failure have shown significant beneficial effects, in particular on health-related quality of life and sexual function, which were impaired at baseline in the participating cohorts.

**Non-estrogenic approaches to the management of menopausal symptoms**

- Lifestyle and diet modifications may improve both hot flushes and mood. Regular exercise, weight reduction, avoiding too much caffeine and cessation of smoking appear to improve hot flushes. Relaxation techniques, meditation, and pace respiration may help too, although there is relatively very little support for that effect from good clinical trials.
- Plant-derived compounds (i.e. isoflavones, evening primrose, black cohosh and ginseng) are very popular as remedies for vasomotor symptoms, sleep disturbances and bad mood. Although some studies found those products to be helpful, the magnitude of the effect – when present – is small and not much greater than that of placebo.
- The most tested pharmacological alternatives to estrogens are serotonin reuptake inhibitors (SSRI). At their best, SSRIs reduce hot flushes by 50–60% and their effect appears only short-term. The more positive results were seen in breast cancer survivors, whereas the chance for negative results was greater in healthy women. SSRIs improve mood independently of their effect on hot flushes. When used for the treatment of the climacteric syndrome, SSRIs do not adversely affect libido. Withdrawal symptoms may occur after long-term use; thus, SSRIs should not be stopped abruptly.

**GENE FINGERPRINTING – ITS ROLE IN HT**

- Genetic variability may be important in determining efficacy of therapy as well as susceptibility for adverse events. Clinical implications of genomic medicine have been investigated also in menopause medicine.
- Enzyme activity may depend on single nucleotide polymorphism. This was demonstrated in regard to steroid synthesizing enzymes and estrogen metabolizing enzymes (i.e. strains of the cytochrome P system).
- Factor 5 and factor 2 polymorphisms are recognized as strong risk predictors for thrombosis in hormone users.

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Suggested Reading

A more comprehensive list of references will be found in a special Supplement to Climacteric; this will be published in August 2007 and will include full-length articles written by the speakers at the 7th IMS Workshop in Budapest.

General

Exercise
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Hormones and breast cancer
Kuhl H. Is the elevated breast cancer risk observed in the WHI study an artifact? Climacteric 2004;7:319–23

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postmenopausal women with hysterectomy.  
*JAMA* 2006;295:1647–57

**Endometrial safety and bleeding**


**Route of administration and timing of initiation**


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**New products and regimens since 2003**


**Androgens**

Davison SL, Bell R, Donath S, Montalto JG, Davis SR. Androgen levels in adult females: changes with age, menopause, and oophorectomy. *J Clin Endocrinol Metab* 2005;90:3847–53

Burger HG, Papalia M. A clinical update on female androgen insufficiency – testosterone testing and treatment in women presenting with low sexual desire. *Sexual Health* 2006;3:73–8

**Urogynecology**


**Cognition and cognitive aging**


**Alzheimer’s disease**


Henderson VW. Estrogen-containing hormone therapy and Alzheimer’s disease risk: understanding discrepant inferences from observational and experimental research. *Neuroscience* 2006;138: 1031–9

**Osteoporosis**


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Coagulation


Gender-specific characteristics of atherosclerosis in menopausal women


Menopause and stroke


Postmenopausal hormones and coronary artery disease


Grodstein F, Manson JE, Stampfer MJ. Hormone therapy and coronary heart disease: the role of time since menopause and age at hormone initiation. *J Women’s Health* 2006;15:35–44


Non-hormonal therapy


New attitudes to sexuality in the menopause

