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Hormonal Replacement Therapy

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1. Introduction

The increase in life expectancy observed in industrialized countries is also taking place in many developing countries and especially in Asia as fertility and mortality decline. Population aging is expected to become a universal phenomenon in the next few decades. Therefore health care strategies have to be established for the prevention of diseases of the elderly as well as social strategies including living arrangements of older adults [1]. Among health care strategies, the hormonal treatment of postmenopausal women at an early stage has been developed for the prevention of osteoporotic fractures that may occur at an older age, prevention of cardiovascular events and possibly prevention of Alzheimer's disease. The goals of the therapeutic approach is not to increase further longevity but to correct symptoms and prevent diseases related to this decline in hormonal secretion of the menopausal ovary, in order to improve the quality of life of aging women and their families as life expectancy is increasing anyway.

Cardiovascular disease (CVD) and in particular coronary heart disease (CHD) are the leading causes of morbidity and mortality' in women. During the past decades several epidemiological studies suggested the beneficial effect of estrogen that appear to decrease the risk of CVD and CHD by 50% [2–4]. Based on that epidemiological data, secondary prevention trials were conducted in women with established CHD, with the goal of preventing recurrence from heart disease. Unfortunately, two randomized controlled trials (RCT) designed for secondary prevention failed to confirm the expected benefits of hormone replacement therapy (HRT) in populations of women with established heart disease [5,6]. Based on these two studies, the American Heart Association (AHA) has recently recommended against the use of HRT in women with established CHD [7]. Misinterpretations of these recommendations led to the unjustified generalization that women without heart disease would not benefit from HRT. This claim is unjustified as the primary prevention trials are still ongoing and their conclusion still unknown [8].

Further negative claims about HRT have been made with regard to the lack of demonstration of fracture prevention. Most studies conducted with HRT demonstrated the superiority of active therapy over placebo on bone mineral density (BMD) as a surrogate marker for fracture prevention [9]. Only one RCT demonstrated prevention from vertebral fracture recurrence in elderly women. These recent controversies led to the unjustified disinterest for HRT. Also, new therapies targeted at the prevention and treatment of osteoporosis have been made available and have been substituted for HRT following controversies about the risk of breast cancer in HRT users. This review carefully examines the recent data published on HRT, discusses the protective role of estrogen and progestin on risk markers and translates this into clinical paradigms when possible.

The benefits of HRT in postmenopausal women that have been established include the correction of vasomotor symptoms, vaginal atrophy, the decrease in accelerated bone loss and the risk of osteoporosis. The role of HRT in reducing the risk of CHD or of Alzheimer's disease is less well established and contradictory findings led to recent controversies [8]. While the former benefits are readily obtained with short-term courses of therapy, the later benefits will be obtained only with long-term therapy which must be maintained. Despite the well-known benefits of this therapy a low percentage of women are treated and among them only 30% are compliant with therapy. Groeneveld et al. [10] showed that 60% of women continued therapy for less than 6 months and only 8% continued for 2 years. The reasons for poor compliance are not only the fear of breast and endometrial cancer and other side effects, but also the non-acceptance of the withdrawal bleedings associated with the hormonal treatment.

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2. What is Available for HRT? Estrogen, Progestin and Androgen for HRT

2.1. Estrogens

Among the molecules available to the prescriber the natural estrogens are usually preferred to synthetic steroids for substitutive estrogen therapy. The artificial molecules such as ethinyl estradiol (EE) are used in oral contraceptives but no longer in menopausal therapy given their metabolic effects. Natural steroids are preferred for HRT.

The most commonly used natural estrogens are the conjugated equine estrogens (CEE), which are mainly composed of estrone (E1) and estrone sulfate (E1S) and extracted from pregnant mare urine. CEE are commonly prescribed orally but also as vaginal creams.

17β Estradiol (E2) has been successfully micronized and was shown to be active over 24 hours when given orally [11]. Estradiol valerate is also being prescribed orally. All these estrogens when given orally result in higher serum levels of E1 and its conjugates than E2. The conversion takes place mainly in the intestinal mucosa [6] and then in the liver, where glucuronidation occurs for about 30% of the initial ingested dose. A rapid urinary and biliary excretion then occurs [12,13]. To avoid this intensive first-pass metabolism other routes of administration of E2 have been sought and delivery through injections, implants, vaginal rings, percutaneous gels, and transdermal systems has been successfully realized. With these systems of parenteral E2 administration, premenopausal serum levels of E2 are achieved with lower levels of E1 resulting in a more physiologic E2/E1 ratio.

2.1.1. Receptor affinity of estrogens. The principal estrogen acting at the cellular and nuclear levels appears to be E2 [14]. Only free E2 unbound to circulating proteins and SHBG is biologically active. After penetration in the target cells it binds to the receptor present in the nucleus, where the nuclear retention allows chromatin modifications and specific messages to be induced. The duration of the nuclear retention of the complex formed by the hormone and its receptor determines the potency of the steroid. It has been shown by Clarck and Peck [15] that the nuclear retention of E2 is far longer than that of E1, which itself is retained longer than estriol (E3). Accordingly, at the cellular level, estrogenic potency is highest for E2 > E1 > E3 [15]. However, continuous delivery of a weak estrogen through infusion or repeated administration results in the same metabolic effects as with more potent estrogens.

2.1.2. Plasma levels after estrogen administration. The levels obtained and the time to reach peak concentrations of circulating estrogen vary greatly according to the type of estrogen used and the route of administration considered.

(a) Oral estrogen. After oral ingestion of 0.625 mg CEE or 1.25 mg E1S or 1 mg micronized E2 similar levels are reached within 4–6 hours, peaking at 30–40 pg/ml of E2 and 150–250 pg/ml of E1 [13]. Levels of E1 as high as 466 pg/ml have been published after oral ingestion of 2 mg micronized E2 [11]. CEE contain various compounds and in addition to E1, up to 20–25% equilin sulfate is present. The latter compound is metabolized to equilenin and 17-hydroxyequilenin. Equilin levels can reach 1.25 pg/mI after ingestion of 1.25 mg CEE. It can be stored in adipose tissue and released for several weeks after treatment withdrawal. These metabolites account for a great part of the estrogenic effect of CEE, and although low levels of E2 are achieved the total amount of estrogens is much higher. It must be kept in mind, however, that the active estrogen at the cellular level is E2. It has been shown that after oral intake of CEE, although E1 was the main circulating estrogen the estrogen present in the cytosolic fraction of endometrial cells is E2[14].

(b) Parenteral estrogens. After parenteral administration of estrogens the first-pass gastrointestinal and liver metabolism is avoided and therefore the plasma levels measured reflect more accurately the dose delivered and absorbed.

- Subdermal implantation of estradiol pellets leads to more sustained serum E2 levels of 50–70 pg/ml [16] after a peak effect at insertion.
- The vaginal epithelium rapidly absorbs estrogens, and E2 can be delivered through silastic rings [17], giving relatively stable E2 levels of 100–150 pg/ml (300–450 pmol/L) over several months. Nash et al. [18] using rings delivering 60–140 mcg/d E2 were effective in correcting menopausal symptoms over 6 months. Mean E2 levels were 123 $\pm$ 48 and 307 $\pm$ 93 pmol/L with the low and high dosage levels, respectively. E1 levels exceeded E2 levels by 1.7 fold in the high dosage ring and 2.6 fold for the lower dosage ring. Vaginal creams of E2 can also lead to high plasma E2 levels [19].
- Skin delivery of estrogen: The first method used for skin delivery of E2 was the *percutaneous* application of E2 dissolved into a water-alcohol solvent in the form of a gel containing 3 mg of E2 per 5 g of gel leading to a plasma concentration of 110–124 pg/ml [20] after repeated administration. The usual recommended dose with this system is 1.5 mg/day, leading to about 50–60 pg/ml in the plasma, which allow the relief of symptoms. The

absorption through the skin is proportional, however, to the surface of application [21], and inadequate dosing may lead to inter- and intra individual fluctuations. This mode of skin delivery of E2 is described as percutaneous administration and should be differentiated from the *transdermal* delivery using transdermal delivery systems (TDS) also called transdermal therapeutic systems (TTS) or patches.

The first generation of rate-controlled reservoir systems has been designed for a twice-weekly application. They were programmed to release, *in vivo*, 0.025, 0.05 and 0.1 mg of E2 per day, according to patient needs [22]. Pharmacokinetic studies in postmenopausal women indicated that therapeutic E2 levels in serum were achieved in less than 4 hours after application and persisted until TTS removal. The E2 /E1 ratio was elevated and maintained close to 1 in the premenopausal range. Further studies have indicated levels in the range of 80–90 pg/ml with the 0.05 mg daily dose [23].

More recently second-generation systems have been introduced using the matrix-dispersion type systems, including systems designed for a once weekly application. The main goal of the development of second generation TTS, was to avoid ethanol in the reservoir system potentially responsible for the skin irritation leading to treatment discontinuation in about 5% of the cases. The new systems have better adhesive properties and a thinner and flat appearance [24].

Further development was then conducted in two directions: First, the addition of a progestin into the same transdermal system was made for sequential or continuous combined therapy. Second, smaller patches have been designed in order to improve their acceptability.

In order to develop smaller patches such as the ''dot'' systems, different enhancers have been used in order to penetrate the skin on a very limited surface area. Therefore, although the application of a steroid on the skin is absorbed proportionally to the surface of application, the technical improvement of the systems would allow the steroid delivery on a much smaller surface than with the first generation of TDS.

- Nasal delivery of estradiol: The benefits of intranasal estrogen therapy have also been examined. It was shown that 300 μg/day of 17β estradiol delivered in an aqueous spray formulation is effective at reducing symptoms, well tolerated and well accepted by the women [25]. The pharmacokinetics of intranasal estradiol differ from other delivery forms. Maximal plasma levels are reached within 10–30 minutes and then decrease to 10% of the peak value after 2 hours. The plasma profile is described as a pulse-like delivery as opposed to the sustained delivery described with transdermal or vaginal administration. Low levels of E1 and SHBG observed in women receiving E2 nasal spray indicate that the first-pass hepatic metabolism is avoided. Although plasma levels are low between pulses, efficacy has been shown by symptom correction equivalent to that of oral E2 and side-effects were not different between oral or nasal treatment [25].

2.2. Pharmacology of progestins used in HRT

The synthetic progestins used in clinical practice are derived either from testosterone (19-nortestosterone derivatives) or from progesterone (17-OH progesterone derivatives and 19-norprogesterone derivatives) [26].

Among the 19-nortestosterone derivatives, the estrane group include norethisterone (NET) and its metabolites, and the gonane group include levonorgestrel (LNG) and its derivatives. The later, including desogestrel (DSG) and etonogestrel, gestodene (GES) and norgestimate (also named norelgestromin), have been referred to as third-generation progestins. By convention the first generation refers to norethynodrel, the first progestin synthesized and the second generation includes NET and LNG [26].

Several new progestins have been synthesized in the last decade [27]. Dienogest is referred to as a hybrid progestin being derived from the gonane group with a 17α-cyanomethyl group [28], and drospirenone derives from spirolactone [29]. The 19-nor derivatives of progesterone are also referred to as ''pure'' progestational molecules as they bind almost exclusively to the progesterone receptor (PR) and do not interfere with the other steroid receptors [27]. This category includes, trimegestone, nomegestrol acetate (NOM Ac), TX525 derived from the former and Nestorone® as well as a new compound related to Nestorone® with a methyl radical in C18 [27,30–32].

Very small structural changes may induce considerable difference on the effects of the progestins. The addition of a double bond in C6–7 position of the hydroxyprogesterone skeleton as well as a deletion of the CH_3 radical in position C19 confers to the molecule of NOM Ac, a higher progestational potency [30] than medroxyprogesterone acetate (MPA). In contrast, Nestorone®, another 19-nor derivative of hydroxyprogesterone, without a CH_3 radical in Position 6 must be administered parenterally due to its rapid hepatic metabolism [32].

2.2.1. Comparative progestational activity of various gestagens. The progestational activity is usually tested using the McPhail Index in immature rabbits, and also the pregnancy maintenance and the ovulation inhibition tests in rats. Using these *in vivo* tests, Nestorone® appears to be the most potent progestin being 10 times more potent than LNG and 100 times more potent than progesterone itself when the molecules are administered subcutaneously [32]. When given orally, NET, medroxy progestrone acetate (MPA) and Drospirenone are more potent than progesterone but less than LNG [27] and NOM Ac is four times more active than MPA [31].

2.2.2. Androgenic activity of progestins. The binding affinity of the various progestins to the sex steroid receptors such as the estrogen receptor (ER) or the androgen receptor (AR) indicate considerable difference between the molecules. However, the binding affinity to the steroid receptors does not always correlate with the *in vivo* tests of estrogenic or androgenic potency.

Using the rat ventral prostate as a source of AR, the relative binding affinity (RBA) of LNG and DSG was 70% and 40% that of testosterone, respectively. In contrast Nestorone® and progesterone did not show any significant binding [32].

The *in vivo* biological assay of androgenicity usually considers the effect of a given compound on the weight increase of the ventral prostate and other male sex organs in immature male rats. Using these models, LNG and 3 keto desogestrel express androgenicity and increase the weight of ventral prostate in a dose-dependent manner, while Nestorone® and progesterone do not induce such effects [32].

In similar experiments, Bullock and Bardin [33] showed also the androgenicity of MPA at high doses. Duc et al. [35] showed no effect of NOM Ac even when administered at very high doses.

2.2.3. Estrogenic activity of progestins. As far as the estrogenic activity of progestins is considered, the uterine weight of ovariectomized immature female rats was significantly increased by LNG but not by Nestorone® at similar doses [32]. Both compounds similarly do not bind to the ER [32].

Therefore, should the classification of progestins be made according to their other activities than the progestational one, the 19-nortestosterone derivatives exert some androgenic activity and only a few exert an estrogenic effect. The 17 hydroxy progesterone derivatives have varying activities; Cyproterone acetate (CPA) is a potent anti-androgenic compound while MPA has slight androgenic activity [33] and also exerts glucocorticoid activity when given at very high doses [34]. Megestrol acetate has 50% less glucocorticoid effects than MPA. Drospirenone more recently synthesized in this class of compounds is essentially an anti-mineralocorticoid progestin and exerts some anti-androgenic activity [29]. Nestorone® binds to the glucocorticoid receptors but does not exert any glucocorticoid activity in the *in vivo* assays [32].

The 19-norprogesterone derivatives appear more specifically progestational and do not possess any androgenic, estrogenic or glucocorticoid activity [32,35]. NOM Ac has a partial anti-androgenic effect but 20 times less than CPA [35].

In summary, all progestins available to the prescriber exert a progestational effect and oppose the proliferative effect of estrogens on the endometrium. However, their progestational potency varies and the dose needed to achieve the effect on the endometrium varies from a few micrograms to several milligrams. In addition, according to their structure and the steroid from which they derive, the different molecules will exert other activities some considered beneficial, some being drawbacks leading to side effects. Given these differences, it appears inappropriate to claim that the side effects of ''progestins'' are a class-effect.

2.2.4. Pharmacokinetic differences between gestagens. Another aspect to consider in the evaluation of the progestagen actions relates to their pharmacokinetic properties and their binding to serum proteins. The comparison of radioactivity recovered in urine and feces after oral or IV administration of a labelled compound would indicate the absolute bioavailability of that compound and determine its absorption via the oral route. The compounds with the highest oral bioavailability are GES, DSG and CPA [27,36].

The half-life of the compounds is also determined by their binding to plasma proteins. As compared with testosterone as a reference, LNG and 3-keto-desogestrel exhibit a significant but lower affinity to the sex hormone binding globulin (SHBG) [32]. While both NET and LNG bind to SHBG, their elimination half-life vary, the terminal half-life ($\beta t1/2$) being around 7–8 hours for NET and up to 26 hours for LNG. In contrast, CPA has a $\beta t1/2$ life of 48 hours [27] and NOM Ac of about 50 hours [31].

Progesterone and Nestorone® do not bind to SHBG and the free fraction of NES would be greater than most of the 19-nortestosterone derived progestins. The oral bioavailability of Nestorone® is only about 10% with a shorter half-life than progestins that bind to SHBG. However, a much slower elimination rate is observed after a chronic subdermal implant [32].

2.3. Androgen

Androgen therapy became recently popular as a treatment of postmenopausal women with sexual

dysfunction. However, no long-term studies are available and accurate methods and scales for assessing efficacy of androgen on libido are lacking. Also definitions of normal sexual function do not exist. The rationale on androgen use in women is based on the loss of androgen production from the ovary in women who undergo ovariectomy and the frequent complaint of loss in sexual interest after surgery. The physiological and biochemical role of androgens on female genital health is controversial. Low dose testosterone patches have been developed and have been shown to improve sexual function [37]. However, the doses required to reach efficacy over placebo on combined scores measuring sexual performance led to supraphysiological levels of dihydrotestosterone (DHT). These high levels may lead to undesirable androgenic side-effects in the long-term treatment. A novel androgen, MENT [38] which does not convert into DHT would appear more suitable for women as it would not stimulate hair growth or clitoral enlargement. This molecule is being tested in various delivery systems.

2.4. Other therapies

Many women choose not to take HRT and women with contraindications to estrogen need alternative options [39]. Based on the discovery of two ER subtypes exerting different tissue-specific effects, selective estrogen receptor modulators (SERMs) have been developed. These molecules are designed to obtain the desired estrogen-like actions on bone and vessels while exerting estrogen antagonistic effects on the breast and uterus. Raloxifen is the lead compound of this category, extensively studied and proven to have an effect in fracture prevention and in decreasing the incidence of new breast cancer [40]. However, in ovariectomized cynomolgous monkeys, no effect of raloxifen was observed against atherosclerosis as compared to estrogen at either low or high doses [39].

For women surviving breast cancer who need alternatives for estrogen a tailored treatment strategy has been recommended in a recent consensus conference [41]. Treatments such as statins have been shown to prevent heart disease and therapies such as biphosphonates, parathormone (PTH) or calcitonin are available for both prevention and treatment of osteoporosis. A once-a-week biphosphonate administration is available for therapy. Also tibolone, a molecule with low estrogenic, low androgenic and low progestational potencies is available in Europe for osteoporosis prevention. These therapies are well accepted by the women who do not wish to have hormone-related withdrawal bleedings.

Research is ongoing on anti bone resorption agents and also on PTH related protein (PTHrp) which is involved in bone loss. Genetics of subjects with high BMD are currently being explored. Most of these new therapies will be available in 5–8 years from now and are all targeted at preventing bone fractures but will not be effective on other symptoms or diseases related to estrogen deficiency.

Low dose of estrogen administered in the vagina from a vaginal ring or creams provides relief of symptoms of urogenital atrophy [42]. Relief from vasomotor symptoms can be obtained with progestin only treatment and especially with megestrol acetate [39].

Phytoestrogens are popular in some countries and soy isoflavones were shown to reduce atherosclerosis in the monkey model. Other herbal therapies available in drugstores are problematic as no quality control is exerted on these products [39].

*3. Benefits of HRT**

3.1. Effects on symptoms and quality of life

The effectiveness of HRT for relief of vasomotor symptoms and vaginal atrophy in the postmenopausal woman is well established. In the US, the most commonly prescribed regimen includes oral conjugated estrogens at a dose of 0.625 mg/d and MPA at 2.5–5 mg/d on a continuous combined regimen or 5–10 mg/day when the progestin is given sequentially 10–14 days per cycle. In Europe the most common treatment is estradiol either given in oral forms of micronized E2 or E2 valerate at doses of 1–2 mg/d, or transdermally in gels or patches at doses of 0.05 or 0.1 mg/d. The progestins prescribed for menopausal treatment are either derived for nortestosterone or essentially derived from progesterone itself or 19-norprogesterone (see above).

More recently large studies showed than lower doses of estrogen were sufficient to correct symptoms. Utian et al. [43] reported the results of the large HOPE study (Women' Health, Osteoporosis, Progestin, Estrogen study) conducted in 2,673 women aged 40–65. Dosages of CEE at 0.45 or 0.3 mg/d combined with MPA 1.5, 2.5 or 1.5 mg/d respectively, were as effective as the commonly prescribed higher doses. Notelovitz et al. [44] showed efficacy of transdermal estradiol at 0.05 mg/d with norethisterone acetate (NETA) also delivered transdermally at doses of 0.14, 0.25 or 0.4 mg/d. Significant reduction in the intensity of hot flushes and sweating were noted with the three doses as compared with placebo. In most studies the effect is seen from the second cycle but is fully achieved after 3 cycles of therapy.

Another benefit of HRT has also been demonstrated.

*See additional late breaking information section.

Quality of life (QoL) scales have been developed specifically for the menopausal women and indicated an improvement in QoL beyond the correction of the symptoms. The loss of drive and energy, sleep problems and mood changes induced by the loss in estrogen secretion are restored by HRT and these benefits have been shown to be significantly superior with estradiol treatment as compared with placebo [45, 46].

3.2. Effects on bone

In the US more than 22 million women are affected by osteoporosis and experience 240,000 hip fractures per year. On average 24% of patients with hip fracture who are age 50 or over die within 1 year [47]. Accelerated bone loss at the menopause actually begins before the onset of amenorrhea. During the 15–20 years following menopause, more than three quarters of bone loss is related to estrogen deficiency and not to aging. Thus ERT is highly recommended to women with risk factors such as women with family history, short/thin stature, smoking, sedentary lifestyle and low calcium intake.

Estrogen effect on the bone mass is well documented. A large number of studies testing several estrogen or estrogen–progestin combinations showed a significant decrease in bone loss with HRT as compared with placebo over 2–3 years of treatment. Bone loss has been measured in these trials by BMD. However not many RCT were conducted to evaluate the decrease in bone fractures.* One study has shown the decrease in risk of vertebral fractures under estrogen [48]. Henry et al. [9] reviewing the RCT published between 1977 and 1995 conclude that the literature fails to address whether estrogen therapy reduces fracture rates. Torgerson et al. [49] conducted a meta analysis of 22 clinical trials including data on more than 8,800 women. The analysis shows that HRT significantly reduces hip and wrist fractures by 40%. The effect of HRT on nonvertebral fractures was significant among women aged less than 60 years (relative risk (RR) 0.67: 95% confidence interval (CI) 0.46–0.98) but not among women older than 60 (RR 0.88; 95% CI 0.71–1.08). Most studies did not evaluate the risk in women with established osteoporosis.

Another study showed that women who smoke were at a higher risk of hip fracture than women who do not smoke. In a study of 4,700 postmenopausal women aged 50–81 years, the risk of hip fracture of current smokers was 1.66 compared with non-smokers [50]. In addition it has been shown previously that women who smoke had less protective effect of oral estrogen on BMD. Jensen et al. [51] studied 136 postmenopausal women treated for one year with one of three different doses of combined estrogen–progestin or placebo. The women were grouped according to smoking status, and serum levels of estrogens before and after treatment. Their results indicate that smokers had reduced levels of estrogen as compared with nonsmokers. The study suggested that an increased hepatic metabolism of estrogens results in lower estrogen levels among smokers. In another study, the response in bone mineral content in smokers and nonsmokers receiving percutaneous estradiol was not different between smokers and nonsmokers [52]. However, there has never been any direct comparative study of oral versus non-oral estrogen therapy in smokers with fracture as the primary end-point.

Enhanced drug metabolism of estrogen in cigarette smokers has been proposed as one of the mechanism to explain the decreased serum levels of estradiol and estrone in smokers who receive oral estrogen. Therefore it is important to explain to patients the impact of smoking on hip fracture risk and to select the appropriate route of administration of estrogen in these women.

3.3. Effects of estrogen on cognition and Alzheimer's disease

Several epidemiological studies, both of case-control or cohort design, indicate that estrogens decrease the incidence of Alzheimer's disease by 20–60% [47]. Postmenopausal women using HRT who had higher estrogen levels scored higher in cognitive tests than non-users. They maintained this cognitive advantage over time with therapy while the non-users had a decrease in their scores after 18 months [53]. The mechanism of action of estrogen in the brain is not fully understood. However, it was shown that estrogen enhances cerebral blood flow and pre- and post-synaptic signal transmission, and protects against oxidative damage. However estrogen did not appear effective as a treatment option for women with established disease [54].

*3.4. Controversies on cardiovascular risk: effects of HRT on risk markers and coronary events.**

The incidence of CVD differs significantly between men and women, in part because of differences in risk factors and hormones. Observational studies have indicated a reduction in CHD of 50% in postmenopausal women receiving HRT as compared with non-users [2,3]. The atheroprotective effects of estrogen were attributed principally to the effects of estrogen on serum lipid concentrations. However, these lipid changes account for only approximately one third of the observed clinical benefits of estrogen [4]. Direct actions of estrogen on blood vessels contribute substantially to the cardiovascular protective effect of estrogen. Estrogen has both rapid and long-term effects on the blood vessel wall. Estrogen influences the bioavailability of endothelial-

*See additional late breaking information section.

derived nitric oxide that promotes vasodilatation. The longer-term effects of estrogen are due in part to changes in vascular-cell gene and protein expression mediated by the ERs, ERα or β isoforms or both [55].

Estrogen deprivation following menopause may affect several of the cardiovascular risk factors [56]. Estrogen replacement therapy (ERT) has been shown to improve insulin sensitivity [57], lower diastolic blood pressure [58] increase HDL_2 levels [59] and stimulate the production of vasodilating factors such as nitric oxide (NO) and prostaglandin by the vessels [60]. Estrogen-induced vasodilatation occurs rapidly and this effect is referred to as a nongenomic effect [55]. Other actions of estrogens occur after several months and are dependent on changes in gene expression. Hence they are referred to as genomic [55]. Progestins down-regulate the ERs and hence may interfere with some of the genomic actions of estrogens.

In a study testing the effects of continuous combined estrogen-progestin replacement therapy compared with unopposed estrogen, it was shown that the unopposed estrogen produced favorable changes in most cardiovascular risk markers that were evaluated [61]. However, the progestin given in combination, NETA, a testosterone derivative, appeared to blunt the reductions in C-peptide and insulin levels produced by unopposed estrogen. It also blunted or reversed the increases in high-density lipoprotein cholesterol and apolipoprotein B levels as compared with estrogen alone [61]. These effects are indeed related to the androgenic properties of the progestin, not to the regimen of HRT. In studies conducted with NOM Ac, no such deleterious effects were found and the progestin did not reverse the beneficial effects of the estrogen [62].

While epidemiological studies conducted from the 1980s onwards have indicated a decreased cardiovascular risk in estrogen users as compared to non-users, RCT of secondary prevention did not support the early findings. The AHA advised against HRT for heart protection on the basis of two studies, the heart and estrogen–progestin replacement study (HERS) and the estrogen replacement and atherosclerosis (ERA) trial [5,6]. Results from these secondary prevention trials were obtained before primary prevention could be established.*

3.4.1. Secondary prevention trials. The HERS study was designed as a randomized, double-blind, placebo-controlled trial to determine whether estrogen (CEE) plus continuous progestagen (MPA) is superior to placebo in preventing recurrent events in 2,763 women with documented coronary disease [5]. These women have been followed-up for 4.1 years on average. The primary outcome was the occurrence of non-fatal myocardial infarction (MI) or CHD death. After 4 years of follow-up, the same number of events was recorded in both the active and the placebo groups; this finding indicates that the combined HRT regimen did not reduce the overall rate of coronary events in postmenopausal women with previous CHD. The relative hazard (RH) for a further event was 0.99 (95% CI 0.8–1.2). In addition, there was no significant difference between groups in any of the secondary outcomes, despite a net decrease in LDL and an increase in HDL cholesterol levels in the hormone-treated group.

In the ERA study, angiography was used to compare the effects of estrogens, with and without MPA, and placebo on the vessels of women with previously documented CHD. No difference was found between the three groups on the progression of coronary atherosclerosis in women with established disease [6].

These are two pertinent clinical studies of secondary prevention and both of them indicated no difference in recurrence of cardiovascular events in women receiving HRT or placebo.

More recently, one of the largest cohort study published to date evaluated clinical outcomes in 114,724 women aged 55 years or older with a documented MI. HRT use was associated with a 35% improvement in the survival rate (OR 0.65; 95% CI 0.59–0.72). This significant reduction in mortality was observed for all age groups [63]. This study, the largest to date indicates a beneficial effect of HRT in contrast to the negative findings of the HERS and ERA studies. However, this study is not a RCT.

3.4.2. Primary prevention trials.* To date, no data exists as regards primary prevention. The woman's health initiative (WHI) trial is ongoing in the US. This study, the largest randomized placebo-controlled study, will examine risks and benefits of HRT in 27,000 women free from CVD. Preliminary results from the first year of therapy indicated a higher number of thromboembolic events in the group receiving active medication. Definite conclusions will not be available before 2005 at the study's conclusion.

The Medical Research Council-HRT study ongoing in Europe is also designed as a long-term primary prevention trial and will enroll postmenopausal women without coronary disease. In both studies the long-term follow-up of treatment and placebo groups will help to answer questions of presumed protective effects of HRT using CEEs and MPA, in preventing CVD and CHD. It would be inappropriate to extend the results of these trials to HRT in general, as the results will relate

*See additional late breaking information section.

specifically to the type of HRT used in each study. Different progestins may produce different results. Unfortunately, most of the large ongoing trials have selected the same HRT regimen for their study designs, thus preventing comparison of different regimens.

3.4.3. Venous thromboembolism (VTE). HRT has been shown to increase the risk of VTE during the first year of use of therapy. In observational studies the RR found for HRT users was up to 2.7 whether the treatment was oral or parenteral and whether progestin was or was not administered with the estrogen [64]. The WHI study, published a 3-year interim data indicating that women who took ERT/HRT continued to have more incidence of MI, stroke and embolism than placebo recipients. The incidence remains, however, lower than expected for the population at large.

4. Risks of HRT

4.1. Ovarian cancer[1]

A large prospective study of the American cancer Society following 211,581 postmenopausal women over 14 years has indicated an increased risk in ovarian cancer mortality in users of estrogen for 10 or more years (RR 2.2; 95% CI 0.99–1.37) [65]. The study begun in 1982 and therefore most of the women receiving estrogen were likely to receive high doses of unopposed estrogen. In contrast the Center for Diseases Control and Prevention published a meta-analysis of 15 epidemiological studies indicating a borderline association between estrogen use and epithelial ovarian cancer (OR 1.3; 95% CI 1.0–1.6), with no dose–response relationship [66]. Whether the data applies for women receiving modern HRT regimen using low doses of estrogen combined with progestin is not clear.

4.2. Endometrial disease; hyperplasia and cancer

An associated risk of endometrial hyperplasia, possibly leading to uterine carcinoma, with long-term use of ERT alone has been documented [67–69]. Statistics published in 1980 showed a continuous rise in the incidence of endometrial cancer in the United States beginning on the West Coast in the mid 1960s, and elsewhere in the United States during the early 1970s [67]. Researchers linked this rise to, among other factors, the use of unopposed estrogen therapy that had become more prevalent during that time for the treatment of various postmenopausal symptoms. An increase was also seen in the incidence of endometrial hyperplasia, the progression of which was associated with the development of endometrial carcinoma. Unopposed estrogen therapy is strongly related to endometrial risk, but cyclic combined HRT appears to largely or totally reduce this side-effect, if the progestin is prescribed for at least 14 days per cycle [68].

Additional research during the late 1970s and early 1980s demonstrated that hyperplasic endometrial tissues contained a higher concentration of progestin receptors, compared with normal uterine tissue and that the addition of progestins to estrogen therapy reduced the risk of development of atypical hyperplasia of the endometrium [70].

Since these publications, the addition of a progestin to the estrogen therapy has been developed in order to antagonize the effects of estrogen on the endometrium and to prevent the development of endometrial hyperplasia [71]. A decrease in the risk of endometrial carcinoma has also been demonstrated with the sequential administration of a progestin together with the estrogen treatment [68,72].

Sequential therapy would induce in most cases secretory transformation of an estrogen-primed endometrium. Continuous combined therapy using both steroids, an estrogen and a progestin in a continuous uninterrupted administration, would rather transform the endometrial tissue into an atrophic state [73]. In both cases the progestin will prevent the proliferation of the endometrium.

4.2.1. Consequences of progestin treatment on bleeding patterns. All regimens with a sequential addition of progestin between 12–14 days per month of estrogen treatment induce regular bleeding when the progestin sequence is completed. However, many women do not readily accept this withdrawal bleeding. In order to improve acceptability of the treatment and compliance with long-term use, new schedules of therapy have been introduced with the goals of getting a bleed-free cycle together with endometrial protection. By using a continuous combined regimen of estrogen and progestin, the endometrial tissue becomes atrophic and the withdrawal bleeding should be eliminated leading to amenorrhea in a large percentage of the subjects.

Several regimens of continuous combined therapy with various estrogens and progestins have been tested [73–75]. In all studies, the authors showed a high rate of amenorrhea in the subjects receiving continuous combined therapy, and with time the percentage of subjects with no bleeding increased.

The probability of achieving amenorrhea was greater if HRT is started 12 months or more after menopause [73]. Also the thinner the endometrium at start, the higher the probability of amenorrhea [75]. Endometrial thick-

[1]Additional information: Lacey et al. JAMA 2002;288:334–341. Women using ERT only for 10 or more years were at significantly increased risk of ovarian cancer.

ness measured by ultrasonography is not always correlated with the histology of the endometrium obtained from a biopsy. However, it is now well established that an endometrial thickness below 4 mm at vaginal ultrasound would indicate atrophy of the tissue and there is no need for an additional biopsy [76].

It was shown that the dropout from treatment correlates with the existence of more bleeding days [75]. In a life-table analysis of the time to dropout and percentage of women remaining under therapy, the group of women with a higher rate of amenorrhea was significantly more compliant than the group with a higher rate of bleeding days [75].

*4.3. Breast cancer risk**

One of the major concern of women with HRT is the risk of breast cancer. A large epidemiological study published by the Collaborative group in Oxford in 1997, analyzed all the individual data from most of the epidemiological studies available and with sufficient power [77]. The study included 17,000 cancer cases and 32,000 controls. Breast cancer risk in HRT users was found at a RR of 1.14 as compared with non-users (95% CI 1.08–1.20). With increased duration of use, the RR increased with a significant trend at $P \leq 0.003$. The risk increases by 2.3% per each year of use (95% CI 1.1–3.6%). This increase in risk was essentially observed in women who were current users at the time of diagnosis or having stopped treatment for 5 years. Therefore long-term use beyond 15 years carry a risk of 1.6 (95% CI 1.3–1.9). Moreover, a significant increase in risk is observed in lean women (BMI^2) receiving HRT for more than 5 years.

In this large study the type of treatment was known for only 39% of the users and 80% received estrogen only. No difference in risk was found between users of estrogen or combined estrogen plus progestin. This study, the largest to date indicate that for 1,000 women starting HRT at age 50 and using it for 10 years, six additional cases of breast cancer would be due to HRT. For a duration of 15 years of HRT, 12 additional cases would be expected.

More recent studies indicated a higher risk in users of combined treatment [68,78–80]. In all these studies HRT use for 5 years and greater increase the risk of breast cancer and the risk appears higher in women who use combined HRT. However in all of these cohorts the percentage of users of combined HRT is rather low. In the study of Schairer et al. [78], the percentage of women in the cohort who received combined HRT was only 4%. Also 5% of that cohort had unknown therapy. Had these 5% used estrogen alone or combined therapy, this might have changed the results for each category. Also there is no information about the risk factors of the women in that cohort, which make the results difficult to interpret.

Another interesting result from the recent studies is that of the schedule of the combined HRT regimen used by the women, either on a sequential basis or as a continuous combined treatment. While Ross et al. [79] indicate a lower risk in women using continuous combined regimen, Magnusson et al. [80] found the opposite results and a lower risk in women under sequential therapy. The type of HRT received in the Swedish cohort [80] included fixed combinations made of oral estradiol or estradiol valerate associated with NET or LNG progestins while Ross et al. cohort [79] included mostly women receiving CEE and MPA. It has been shown that oral estradiol is converted into E1 and levels of E1 up to 466 pg/ml were found in the plasma of women having received 2 mg oral estradiol [11]. Therefore the total estrogenic environment is much higher with the type of HRT described in Magnusson et al. [80] than in the cohort of Ross et al. [79]. The opposite findings in both cohorts according to the schedule of therapy make it difficult to draw definite conclusions.

The use of progestins in combination with estrogen is a rather recent phenomenon. Although combination therapy was routinely used in France and Germany, it has only been used since the early 1980s in Scandinavia and the United Kingdom. Only 10 years later, after the FDA recommended the addition of a progestin to various estrogen regimens, did combined HRT use begin to be widespread in the United States of America.

The results of large prospective studies published in the late 1990s reported on the effects of combined HRT prescribed 10 years earlier. It is therefore not surprising that the percentage of progestin users in the recently published cohort studies is still much lower than the ones of unopposed estrogen therapy.

Several compounds with progestional activity have been used for HRT. As described earlier, small differences in the structure of the molecules may lead to pronounced differences in activities, some progestins exerting androgenic effects and some exerting estrogenic or glucocorticoid like activities. In the United States, the main progestin used for HRT has been MPA a derivative of progesterone exerting slight androgenic effects and glucocorticoid like activity.

In Europe, several other progestins have been used. In Scandinavian countries the main HRT combinations contain NETA or LNG both deriving from testosterone and exhibiting some androgenic properties. In Southern Europe, including France retro progesterone, chloradinone acetate and 19-norprogesterone derivatives have been preferred for HRT and prescribed since the late 1980s.

*See additional late breaking information section.

While most progestins do not bind to the ER [27], Catherino et al. [81] have shown that some progestins such as norethynodrel, LNG or GES stimulate MCF7 cells pro-liferation in *in vitro* experiments. These authors have shown that this effect was an ER-mediated mechanism. In contrast, progestins derived from progesterone such as MPA, promegestone or NOM Ac did not induce cell multiplication in the same cell lines [82]. Plu-Bureau et al. [83], treating premenopausal women with benign breast disease with progestins, showed that 19-nortestosterone derivatives were associated with a lower risk of breast cancer than untreated women (RR 0.48; 95% CI 0.25–0.90). Therefore, different progestins may induce different effects on the breast cells [81–84].

Also, the type of estrogen prescribed together with the progestin makes a difference. Oral micronized estradiol or estradiol valerate lead to high circulating levels of E1, through liver metabolism of the compound [11]. Therefore, the total amount of circulating estrogen is high in these women and the balance between the estrogenic and the progestogenic components of HRT varies from one therapeutic regimen to the other.

With current low-dose regimens, the risk of exposure of breast cells to high estrogenic stimulation is minimal. It appears from the epidemiological data that the risk is absent for 5 years of therapy and slightly increased after 10–15 years of HRT.* However the mortality is significantly decreased in women who have breast cancer while under treatment suggesting a better differentiation of the breast cells [77].

The position paper of the International Menopause Society (IMS) on HRT and Cancer [85] concluded that sex steroids are not direct carcinogens as they do not induce direct damage of the DNA. The importance of differences in bioavailability and tissue effects of sex steroids used in HRT was also highlighted. Therefore not all forms of HRT can be considered jointly in terms of breast cancer risk. This issue has been identified by the IMS as one area of future research in the fields.

5. *Risk-benefit equation*

Use of HRT for a few years at around the time of the menopause will relieve symptoms, improve quality of life and not lead to decrease or increase in osteoporosis, CVD or cancer. With long-term use the balance between risks and benefits is not overwhelming in any direction. For many women the benefits far outweigh the risks while for others the risks outweigh the benefits. The use of HRT has to be tailored to the needs and risk factors of each individual. The clinical synthesis conference published in the *Lancet* in 1999 [86] concludes that the decision to start therapy should be taken by the woman after a sensitive consultation with her physician to ensure her understanding of the risks and benefits of both short-term and long-term therapy. Several analyses have shown that HRT use prolongs life among postmenopausal women [47]. Use of HRT is expected to prolong life expectancy in most women at great risk of osteoporosis but low risk of breast cancer.

The negative results obtained from some RCT in the treatment of women with established disease such as atherosclerosis or Alzheimer's disease should not be extrapolated to a lack of preventive effect in women without such conditions. A more recent RCT showed a slower progression of subclinical atherosclerosis in postmenopausal women receiving E2 than in women receiving placebo. This positive result stands in opposition to the previous RCT and supports the protective effect of estradiol in women without preexisting overt CVD [87]. Therefore, and as far as CVD is concerned, a large volume of data shows a protective effect of estrogen in women and it would be inappropriate to rely only on the conclusions of the HERS study to make clinical decisions [8].*

Prescribing molecules close to the natural hormones, estradiol and progesterone with no deleterious action on the metabolic factors would be preferable and excluding women with a high risk of breast cancer would be more cautious. However in women with previous breast cancer HRT may bring additional benefits and this area needs further research.

The long-term benefits of therapy can only be obtained with long-term use of HRT and compliance. In order to enhance continuation rates for HRT the North American Menopause Society has established a consensus paper including recommendations [88]. Among these recommendations counseling the woman on the risk/benefits of therapy and involving her in the decision process are of paramount importance. Each woman is unique and has her own risk profile. Therefore HRT should be tailored to her profile and her preferences and adjusted according to her response. Following these recommendations should increase compliance and bring health benefits with minimal risks and enhance the overall quality of life of the postmenopausal woman.

*See additional late breaking information section.

References

1. Bongaarts J, Zimmer Z. Living arrangements of older adults in the developing world: An analysis of DHS household surveys. *J Gerontol Soc Sci* 2002;57B:5145–5147.

2. Stampfer MJ, Colditz GA. Estrogen replacement therapy and coronary heart disease: A quantitative assessment of the epidemiologic evidence. *Prev Med* 1991;20:47–63.
3. Colditz GA. Menopause and the risk of coronary heart disease in women. *N Engl J Med* 1987;316:1105–1110.
4. Bush TL, Barret-Connor E, Cowan LD, Wallace RB, Suchindran CM, Tyroler HA, Rifkind BM. Cardiovascular mortality and noncontraceptive use of estrogen in women: results from the Lipid Research Clinic Program follow-up study. *Circulation* 1987;75:1102–1109.
5. Hulley S, Grady D, Bush T, Furberg C, Herrington O, Riggs B, Vittinghoff E. Heart and estrogen/progestin replacement study (HERS) research group. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. *JAMA* 1998;280:605–613.
6. Herrington DM, Reboussin DM, Bosnihan KB, Sharp PC, Shumaker SA, Snyder TE, Furber CD, Kowalchuk GJ, Stuckey TD, Rogers WJ, Givens DH, Waters D. Effects of estrogen replacement on progession of coronary-artery atherosclerosis. *N Engl J Med* 2000;343:522–529.
7. Mosca L, Collins P. Hormone replacement therapy and cardiovascular disease: A statement for Healthcare professionals from the American Heart Association. *Circulation* 2001;104:499–503.
8. Mendelsohn ME, Karas RH. Editorial: The time has come to stop letting the HERS tale wag the dogma. Editorial: *Circulation* 2001;104:2256–2257.
9. Henry D, Robertson J. A systematic review of the skeletal effects of estrogen therapy in postmenopausal women. I. An assessment of the quality of randomized trials published between 1977 and 1995. *Climacteric* 1998;1:92–111.
10. Groeneveld FP, Bareman FP, Barentsen R, Dokter HJ, Drogendijk AC, Hoes AW. Duration of hormonal replacement therapy in general practice; a follow-up study. *Maturitas* 1998;29(2):125–131.
11. Yen SSC, Martin PL, Burnier AM, Czekala NM, Greney MO, Jr., Callantine MR. Circulating estradiol, estrone and gonadotropin levels following the administration of orally active 17b-estradiol in postmenopausal women. *J Clin Endocrinol Metab* 1975;40:518–520.
12. Sitruk-Ware R. Pharmacology of estrogens. Different routes of administration, oral versus transdermal. In: Oettel M, Shillinger E, (eds). *Handbook of Experimental Pharmacology, vol 135, Estrogen and Antiestrogens*. Heidelberg: Springer Verlag, 1999;247–257.
13. Barnes RD, Lobo RA. Pharmacology of estrogens. In: Mishell DR, Jr., ed. *Menopause Physiology and Pharmacology*, Chicago Year Book Medical Publishers, 1987;301–315.
14. Gurpide E. Metabolic influences of the action of estrogens; therapeutic implications. *Pediatrics* 1978;62(Suppl.):1114–1120.
15. Clarck JH, Peck EJ, Jr. Female sex steroids. receptors and function. *Monographs on Endocrinology.* New York: Springer, 1979.
16. Stanczyk FZ, Shoupe D, Nunez V, Macias-Gonzales P, Vijod MA, Lobo A. A randomized comparison of non-oral estradiol delivery in postmenopausal women. *Am J Obstet Gynecol* 1988;159:1540–1546.
17. Mishell DR, Jr., Moore DE, Roy S, Brenner PF, Page MA. Clinical performance and endocrine profiles with contraceptive vaginal rings containing a combination of estradiol and d-norgestrel. *Am J Obstet Gynecol* 1978;130:55–62.
18. Nash HA, Sanchez-Alvarez F, Mishell DR, Jr., Fraser IS, Maruo T, Harmon TM. Estradiol-delivering vaginal rings for hormone replacement therapy. *Am J Obstet Gynecol* 1999;181(6):1400–1406.
19. Rigg LA, Hermann H, Yen SSC. Absorption of estrogens from vaginal creams. *N Engl J Med* 1978;298:195–197.
20. Sitruk-Ware R, De Lignieres B, Basdevant A, Mauvais-Jarvis P. Absorption of percutaneous oestradiol in postmenopausal women. *Maturitas* 1980;2:207–211.
21. Marty JP, James M, Hajo N, Wepierre J. Percutaneous absorption of oestradiol and progesterone: pharmacokinetic studies. In: Mauvais-Jarvis P, Vickers CFH, Wepierre J, (eds). *Percutaneous Absorption of Steroids*. London: Academia Press, 1980;205–218.
22. Powers MS, Schenkel L, Darley PE, Good WR, Balestra JC, Place VA. Pharmacokinetics and pharmacodynamics of transdermal dosage forms of 17β-estradiol: comparison with conventional oral estrogen used for hormone replacement. *Am J Obstet Gynecol* 1985;152:1099–1106.
23. Erkkola RU, Hirvonen El, Juntunen K, Saastamoinen IA, Tuimala RI, Rinne R, Paakkari I. Comparison of transdermal to oral hormone replacement therapy. *Eur Menopause J* 1995;2:21–27.
24. Reginster JY, Donazzlo Y, Brion N, Lins R. Estradiol pharmacokinetics after transdermal application of patches to postmenopausal women: matrix versus reservoir patches. *Climacteric* 2000;3:168–175.
25. Studd J, Pornel B, Marton I, Bringer J, Varin C, Tsouderos Y, Christiansen C, for the Aerodiol Study Group. Efficacy and acceptability of Intranasal 17β-oestradiol for menopausal symptoms: randomized dose–response study. *Lancet* 1999;353:1574–1578.
26. Henzl MR, Edwards JA. Pharmacology of progestins: 17β-hydroxyprogesterone derivatives and progestins of the first and second generation. In: Sitruk-Ware R, Mishell DR, Jr. (eds), *Progestins and Antiprogestins in Clinical Practice*. New York: Marcel Dekker, 2000;101–132.
27. Sitruk-Ware R. Progestogens in HRT. New molecules. *Menopause* 2002;9:6–15.
28. Oettel M, Holz C. Hybrid Progestins: the example of Dienogest. In: Sitruk-Ware R, Mishell DR, Jr. (eds), *Progestins and Antiprogestins in Clinical Practice*. New York: Marcel Dekker, 2000;163–178.
29. Oelkers W. Foidart JM, Dombrovicz N, Welter A, Heithecker R. Effects of the new oral contraceptive containing an antimineralocorticoid progestogen, drospirenone, on the Renin-Aldosterone System, body weight, blood pressure, glucose tolerance and lipid metabolism. *J Clin Endocrinol Metab* 1995;80:1816–1821.
30. Tuba Z, Bardin CW, Dancsi A, Francsics-Czinege E, Molnar C, Csorgei J, Falkay G, Koide SS, Kumar N, Sundaram K, Dukat-Abrok V, Balogh G. Synthesis and biological activity of a new progestogen, 16-methylene-17a-hydroxy-18-methyl-10-norpregn-4ene-3, 20-dione acetate. *Steroids* 2000;65:266–274.
31. Paris J, Thevenot R, Bonnet P, Granero M. The pharmacological profile of TX 066 (17a-acetoxy-6methyl-19-nor-4, 6-pregna-diene-3, 20-dione) a new oral progestative. *Drug Res* 1983;33:710–715.
32. Kumar N, Koide SS, Tsong YY, and Sundaram K. Nestorone®: a progestin with a unique pharmacological profile. *Steroids* 2000;65:629–636.
33. Bullock LP, Bardin CW. Androgenic, synadrogenic and antiandrogenic actions of progestins. *Ann NY Acad Sci* 1977;286:321–330.
34. Hellman L, Yoshida K, Zumoff B, Levin J, Kream J and Fukushima DK. The effect of medroxyprogesterone acetate on the pituitary-adrenal axis. *J Clin Endocrinol Metab* 1976;42:912–917.
35. Duc I, Botella J, Bonnet P, Fraboul F, Delansorne R, Paris J. Antiandrogenic properties of nomegestrol acetate. *Arzneim Forsch/Drug Res* 1995;45(1):70–74.
36. Wilde MI, Balfour JA. Gestodene. A review of its pharmacology, efficacy and tolerability in combined contraceptive preparations. *Drugs* 1995;50:364–395.
37. Shifren JI, Braunstein GD, Simon JA, Casson PR, Buster JE, Redmond GP, Burki RE, Ginsburg ES, Rosen RC, Leiblum SR,

Jones KP, Daugherty CA, Caramelli KE, Mazer NA. Transdermal testosterone in women with impaired sexual function after oophorectomy. *N Engl J Med* 2000;343:682–688.
38. Kumar N, Didolkar AK, Monder C, Bardin CW, Sundaram K. The biological activity of 7α-Methyl-19-Nortestosterone is not amplified in male reproductive tract as is that of testosterone. *Endocrinology* 1992;130:3677–3683.
39. Pinkerton J, Santen R. Alternatives to the use of estrogen in postmenopausal women. *Endocrine Rev* 1999;20(3):308–320.
40. Burger HG. Selective oestrogen receptor modulators. *Horm Res* 2000;53(3):25–29.
41. 1998 Consensus Statement: treatment of estrogen deficiency symptoms in women surviving breast cancer. *J Clin Endocrinol Metab* 2000;83:1993–2000.
42. Sitruk-Ware R, Thomas JL. Traitement local de l'atrophie urogénitale après la menopause. *Praxis* 1997;86:1245–1248.
43. Utian WH, Shoupe D, Bachmann G, Pinkerton JV, Pickar JH. Relief of vasomotor symptoms and vaginal atrophy with lower doses of CEE and medroxyprogesterone acetate. *Fertil Steril* 2001;75:1065–1075.
44. Notelovitz M, Cassel D, Hille D, Furst KW, Dain MP, Vandepol C, Skarinsky D. Efficacy of continuous sequential transdermal estradiol and norethindrone acetate in relieving vasomotor symptoms associated with menopause. *Am J Obstet Gynecol* 2000;182(1 Pt 1):7–12.
45. Limouzin-Lamothe M, Mairon N, Joyce CRB, Gal ML. Quality of life after the menopause: Influence of hormonal replacement therapy. *Am J Obstet Gynecol* 1994;170(2):618–624.
46. Wiklund I, Karlberg J, Mattson LA. Quality of life of postmenopausal women on a regimen of transdermal estradiol therapy: a double-blind placebo-controlled study. *Am J Obstet Gynecol* 1993;168:824–830.
47. Burkman RT, Collins JA, Greene RA. Current perspectives on benefits and risks of hormone replacement therapy. *Am J Obstet Gynecol* 2001;185(2):S13–S23.
48. Lufkin EG, Wahner HW, O'Fallon WM, Hodgson SF, Kotowicz MA, Lane AW, Judd HL, Caplan RH, Riggs BL. Treatment of postmenopausal osteoporosis with transdermal estrogen. *Ann Intern Med* 1992;117(1):1–9.
49. Torgerson DJ, Bell-Syer SE. Hormone replacement therapy and prevention of nonvertebral fractures: a meta-analysis of randomized trials. *JAMA* 2001;285(22):2891–2897.
50. Baron JA, Farahmand BY, Weiderpass E, Michaelsson K, Alberts A, Persson I, Ljunghall S. Cigarette smoking, alcohol consumption, and risk of hip fracture in women. *Arch intern Med* 2001;161(7):983–988.
51. Jensen J, Christensen C, Rodbro P. Cigarette smoking, serum estrogens, and bone loss during hormone replacement therapy early after menopause. *N Engl J Med* 1985;313:973–975.
52. Jensen J, Christiansen C. Effects of smoking serum lipoproteins and bone mineral content during postmenopausal hormone replacement therapy. *Am J Obstet Gynecol* 1988;159:820–825.
53. Carlson LE, Sherwin BB. Higher levels of plasma estradiol and testosterone in healthy elderly men compared with age-matched women may protect aspects of explicit memory. *Menopause* 2000;7:168–177.
54. Mulnard RA, Cotman CW, Kawas C, Van Dyck CH, Sano M, Doody R. Estrogen replacement therapy for the treatment of mild to moderate Alzheimer disease: A randomized controlled trial. *JAMA* 2000;283:1007–1015.
55. Mendelsohn ME, Karas RH. The protective effects of estrogen on the cardiovascular system. *N Engl J Med* 1999;340(23):1801–1811.
56. Rich-Edwards JW, Mason JE, Hennekens CH, Buring JE. The primary prevention of coronary heart disease in women. *N Engl J Med* 1995;332:1758–1766.
57. De Cleyn K, Buytaert P, Coppens M. Carbohydrate metabolism during hormonal substitution therapy. *Maturitas* 1989;11:235–242.
58. Pang SC, Greendale GA, Cedar MI, Cambone AC, Lozano K, Eggena P, Judd HL. Long term effects of transdermal estradiol with and without medroxyprogesterone acetate. *Fertil Steril* 1993;59:76–82.
59. The writing group for the PEPI trial. Effects of estrogen or estrogen/progestin regimens on heart disease risk factors in postmenopausal women: the Postmenopausal Estrogen/Progestin Intervention (PEPI) Trial. *JAMA* 1995;273:199–208.
60. Ylikorkala O, Cacciatore B, Paakkari I, Tikkanen MJ, Viinikka L, Toivonen J. The long term effects of oral and transdermal postmenopausal hormone replacement therapy on nitric oxide, endothelin-1, prostacyclin, and thromboxane. *Fertil Steril* 1998;69(5):883–888.
61. Davidson MH, Maki KC, Marx P, Maki AC, Cyrowski MS, Nanavati N, Arce JC. Effects of continuous estrogen and estrogen-progestin replacement regimens on cardiovascular risk markers in postmenopausal women. *Arch Intern Med* 2000;160(21):3315–3325.
62. Williams JK, Cline JM, Honore EK, Delansorne R, Paris J. Coadministration of nomegestrol acetate does not diminish the beneficial effects of estradiol on coronary artery dilator responses in non human primates. *Am J Obstet Gynecol* 1998;179:1288–1294.
63. Shlipak M, Angeja BG, Go AS, Frederick PD, Canto JG, Grady D, for the National Registry of Myocardial Infarction-3 Investigators. Hormone therapy and in-hospital survival after myocardial infarction in postmenopausal women. *Circulation* 2001;104:2300–2304.
64. Perez-Gutthann S, Garcia-Rodriguez LA, Castelsague J, Duque-Oliart A. A population based case-control study. HRT and the risk of venous thromboembolic event. *BMJ* 1997;314:796–800.
65. Rodriguez C, Patel AV, Calle EE, Jacob EJ, Thun MJ. Estrogen replacement therapy and ovarian cancer mortality in a large prospective study of US women. *JAMA* 2001;285:1460–1465.
66. Coughlin SS, Giustozzi A, Smith SJ, Lee NC. A meta-analysis of estrogen replacement therapy and risk of epithelial ovarian cancer. *J Clin Epidemiol* 2000;53:367–375.
67. Gray L, Christerpherson W, Hoover R. Estrogens and endometrial carcinoma. *J Am Coll Obstet Gynecol* 1977;49:385–389.
68. Persson I, Weiderpass E, Bergkvist L, Bergstrom R, Schairer C. Risks of breast and endometrial cancer after estrogen and estrogen-progestin replacement. *Cancer Causes Controls* 1999;10:253–260.
69. LaVecchia C, Brinton L, McTiernan A. Menopause, hormone replacement therapy and cancer. *Maturitas* 2001;39:97–115.
70. Janne O, Kauppila A, Kontula K. Female steroid receptors in normal, hyperplastic and carcinomatous endometrium. The relationship to serum steroid hormones and gonadotropins and changes during medoxyprogesterone acetate administration. *Int J Cancer* 1979;24:545.
71. Woodruff D, Pickar JH. Incidence of endometrial hyperplasia in post-menopausal women taking conjugated estrogens (Premarin) with medroxy progesterone acetate or conjugated estrogens alone. *Am J Obstet Gynecol* 1994;170:1213–1223.
72. Beresford SAA, Weiss NS, Voigt LF, McKnight B. Risk of endometrial cancer in relation to use of oestrogen combined with cyclic progestagen therapy in postmenopausal women. *Lancet* 1997;349:458–461.
73. Archer D, Pickar JH, Bottiglioni F. Bleeding patterns in postmenopausal women taking continuous combined or sequential regimens of conjugated estrogens with medroxyprogesterone acetate. Menopause Study Group. *Obstet Gynecol* 1994;83:686–692.

74. AinMelk Y. Comparison of two continuous combined estrogen progestogen regimen in postmenopausal women: a randomized trial. *Fertil Steril* 1996;66:962–968.
75. Ödmark IS, Jonsson B, Bäckström T. Bleeding patterns in postmenopausal women using continuous combination hormone replacement therapy with conjugated estrogen and medroxyprogesterone acetate or with 17β-estradiol and norethindrone acetate. *Am J Obstet Gynecol* 2001;184:1131–1138.
76. Langer RD, Pierce JJ, O'Hanlan KA, Johnson SR, Espeland MA, Trabal JF, Barnabei VM, Merino MJ, Scully RE. The Postmenopausal Estrogen/Progestin Interventions Trial. Transvaginal ultrasonography compared with endometrial biopsy for the detection of endometrial disease. *N Engl J Med* 1997;337:1792–1798.
77. Collaborative group on hormonal factors in breast cancer. Breast cancer and hormone replacement therapy: collaborative reanalysis of data from 51 epidemiological studies of 52,705 women with breast cancer and 108,411 women without breast cancer. *Lancet* 1997;350:1047–1059.
78. Schairer C, Lubin J, Troisi R. Menopausal estrogen and estrogen-progestin replacement therapy and breast cancer risk. *JAMA* 2000;283:485–491.
79. Ross RK, Paganni-Hill A, Wan PC, Pike MC. Effect of hormone replacement therapy on breast cancer risk: estrogen versus estrogen plus progestin. *J Natl Cancer Inst* 2000;92:328–332.
80. Magnusson C, Baron JA, Correira N. Breast cancer risk following long term oestrogen and oestrogen–progestin replacement therapy. *Int J Cancer* 1999;31:339–344.
81. Catherino WH, Jeng MH, Jordan VC. Norgestrel and gestodene stimulate breast cancer cell growth through an oestrogen receptor mediated mechanism. *Br J Cancer* 1993;67:945–952.
82. Catherino WH, Jordan VC. Nomegestrol acetate, a clinically useful 19-norprogesterone derivative which lacks estrogenic activity. *J Steroid Biochem Mol Biol* 1995;55:239–246.
83. Plu-Bureau G, Lê M, Sitruk-Ware, Thalabard JC, Mauvais-Jarvis P. Progestogen use and risk of breast cancer in a cohort study of premenopausal women with benign breast disease. *Br J Cancer* 1994;70:270–277.
84. Santen R, Pinkerton JV, McCartney C, Petroni GR. Risk of breast cancer with progestins in combination with estrogen as hormone replacement therapy. *J Clin Endocrinol Metab* 2001;86:16–23.
85. Genazzani AR, Gadducci A, Gambacciani M. Controversial issues in climacteric medicine II: Hormone replacement therapy and cancer. *Maturitas* 2001;40:117–130.
86. Clinical Synthesis Panel on HRT. Hormonal replacement therapy. *Lancet* 1999;354:152–155.
87. Hodis HN, Mack WJ, Lobo RA, Shoupe D, Sevanian A, Mahrer PR, Selzer RH, Liu Cr CR, Liu Ch CH, Azen SP: Estrogen in the prevention of atherosclerosis trial research group. Estrogen in the prevention of atherosclerosis. A randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 2001 (Dec);135:939–953.
88. The North American Menopause Society. Achieving long-term continuance of menopausal ERT/HRT: Consensus opinion of the North American Menopause Society. *Menopause* 1998;5:69–76.

Late-breaking Information

The National Heart, Lung and Blood Institute (NHLBI) of the National Institutes of Health (NIH) announced on July 9, 2002 the early end to the Women's Health Initiative (WHI) study on the results of estrogen plus progestin in healthy, postmenopausal women. The study was halted due to an increased risk (26 percent) of breast cancer and a lack of overall benefit. This large randomized controlled multi-center trial (RCT) compared the response to conjugated equine estrogens (CEE) 0.625-mg/d and medroxyprogesterone acetate (MPA) 2.5 mg/d given continuously ($n = 8{,}506$) with placebo ($n = 8{,}102$). The major outcomes of the study comparing women taking a placebo pill to women on estrogen plus progestin were as follows:

Estimated Hazard ratios (HRs):

- Breast cancer risk 1.26 [95% confidence interval (CI) 1.00–1.59]
- Coronary heart disease (CHD) risk 1.29 [CI 1.02–1.63]
- Stroke risk 1.41 [CI 1.07–1.85]
- Pulmonary embolism risk 2.13 [CI 1.39–3.25]

As benefits, the study results indicate a decreased risk of hip fracture (0.66 [95% CI 0.45–0.98]) and of colorectal cancer (0.63 [95% CI 0.43–0.92]).

In absolute numbers these increases correspond to 8 more cases of breast cancer, 7 more cases of coronary events, 8 more strokes and 8 more women with pulmonary embolism. There were also 6 fewer cases of colon cancer and 5 fewer cases of hip fractures (in 10,000 person years).

The estrogen only arm of the WHI trial has not been stopped. In that arm women are receiving either CEE 0.625 mg/d or placebo. To date no increased risk has been observed, allowing the study to continue.

It would be inappropriate to extend the finding to all HRT preparations as the doses and type of molecules vary in terms of their pharmacological action as described in this article. Indeed the WHI study results are valid only for the HRT preparation used in that study.

As far as breast cancer risk is concerned, the percent increase observed in this study corresponds to previous observational studies where a 30% increase in risk was observed for users of estrogen alone or in combination with progestins with no significant difference between groups. The increased risk appeared after 5 years of therapy. In the present WHI trial, the risk appears from the 4th year of therapy. The increased risk in invasive but not in localized breast cancers may indicate that the therapy favors growth of an undetected existing cancer rather than the induction of a new tumor. In addition more than 6,000 women per group who never take HRT before enrollment in the trial were analyzed separately and here the increase in risk was not apparent: 6% increase and not significant [HR 1.06 (CI: 0.81–1.38)]. In contrast, for women with < 5 years of prior use, the HR

was at 2.13 (CI: 1.15–3.94) and for women with 5–10 years of prior use further increased at 4.61 (CI: 1.01–21.02). Therefore the risk appeared only in women who previously had used HRT for various durations. It is therefore inappropriate to conclude that the risk for breast cancer appears at 4 years of therapy. The risk is cumulative and would appear after 5 years of therapy and this has been already shown by the epidemiological studies.

DMPA, used for many years as a contraceptive (in the absence of estrogen treatment, and in younger women) does not increase breast cancer. Also MPA in higher doses has been used successfully for the treatment of breast cancer. Therefore it would appear that the combination of MPA with estrogen is more deleterious that the progestin used alone.

The women accepted the 30% increased risk of breast cancer in the light of alleged benefits in prevention of fractures and CHD. The prevention in hip fractures is well demonstrated in the present WHI study although only small numbers are involved. However, the prevention from CHD is not provided with the HRT combination tested.

The study results indicate an increase in Coronary Heart Disease events rather than the expected decrease announced by the previous observational studies. Whether this effect is related to MPA is not so clear-cut. However it is well known that MPA has androgenic and antiglucocorticoid properties and reverses some of the estrogen effect while natural progesterone or other derivatives do not. While other progestins might exert a better action than MPA on the CHD risk, this has not as yet been documented by large RCT.

Recommendations

Soon after the press release from the NIH and the publication of the JAMA article, several statements were issued by various medical societies. All of them agree on the fact that it would be most inappropriate to generalize the results of the WHI to all kinds of therapies. Lower doses of HRT, other routes of administration, other molecules closer to the physiological hormones may not induce the same effects. Whether other large studies of the same scale as the WHI would be funded to document the effects of other HRT combinations is unlikely although much needed.

Use of HRT for up to 5 years at around the time of the menopause will relieve symptoms, improve quality of life and not lead to decrease or increase in osteoporosis, cardiovascular disease or cancer. The increase in thrombotic events is to be expected in the first year of therapy in a subgroup of women at risk. With long-term use over 5 years the balance between risks and benefits is not overwhelming in any direction. The risk for an individual woman should be identified based on her individual health history. For many women the benefits far outweigh the risks while for others the risks outweigh the benefits. The use of HRT and the selection of the molecules to prescribe has to be tailored to the needs and risk factors of each individual.

Writing group for the Women's Health Initiative investigators: Risks and Benefits of Estrogen plus Progestin in Healthy postmenopausal Women. Principal results from the Women's Health Initiative Randomized Controlled Trial. JAMA 2002;288:321–333 with an Editorial by S Fletcher and GA Colidtz JAMA 2002;288:366–368.