HT: Pharmacology Tailored to Women's Health

20

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20.1 Introduction

As many as 80% of women experience subjective menopausal vasomotor symptoms (VMS), and in a number of cases, these are sufficiently unpleasant to significantly impair the quality of life [1, 2]. The frequency and severity of VMS peak in the late perimenopause and early postmenopausal years, with large ethnic and racial variation in prevalence, frequency, and severity of symptoms [3]. Obesity has been found to be a key risk factor for perimenopausal, but not postmenopausal VMS. Women with higher abdominal adiposity, particularly subcutaneous adiposity, are more likely to report VMS in the early and late perimenopause [4]. Recent genome-wide association studies (GWAS) have identified over 44 genetic variants that are associated with age of onset of natural menopause. Genes linked with menopause can be classified into three major groups: genes implicated in genome stability (DNA repair), immune function, and mitochondrial biogenesis. Biological and epidemiological data indicate that reproductive performance, age at menopause, and longevity are interlinked through common genetic factors, which play a pivotal role in DNA repair and genome maintenance, which has been linked before with the process of aging [5]. Studies also suggest a possible link between genetic polymorphisms and prevalence and severity of VMS. These involve variants in genes encoding estrogen receptor alpha [6, 7] and single-nucleotide polymorphisms involved in the synthesis and metabolism of estrogens, such as those affecting enzymes (like sulfotransferase and aromatase) related to synthesis of and conversion to more or less potent estrogens [8]. These polymorphisms may alter sex steroid hormone activity, but it is unknown whether these genetic determinants exert their effects centrally or peripherally [9]. Of note the decline in estrogen production has more

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threatening long-term health implications in that it is closely associated with the development of osteoporosis and the increased risk of cardiovascular disease (CVD), the main cause of death in the Western world, and, as a consequence, a major public health issue. Abundant RCTs have demonstrated that estrogen represents the most effective treatment for menopausal symptoms including vasomotor, psychologic, and related issues including impaired cognition, sleep, and irritability, resulting in decreased quality of life [10, 11]. Higher doses are associated with enhanced efficacy. In women with an intact uterus, treatment with estrogen only is associated with an elevated risk of endometrial neoplasia with dose and duration of treatment directly related to the magnitude of this risk. When adequate progestogen is combined with estrogen, risk of endometrial neoplasia is not higher than in untreated women [11]. Oral and transdermal estrogen formulations have comparable efficacy in treating menopausal symptoms [12], and with the exception of estriol products, all systemic estrogen (17 beta estradiol and conjugated estrogen) formulations are approved for treatment of vasomotor symptoms.

However, the Women's Health Initiative (WHI) hormone therapy trials [13, 14], especially the trial involving estrogen plus progestin, completely changed the understanding of the risks and benefits of hormone therapy and reinforced the importance of assessing numerous outcomes. Cardiovascular disease risk was increased rather than decreased as was the risk of thromboembolic disease.

The relationship of hormone therapy to breast cancer was complex and confusing, and for the first time, differences in outcomes other than endometrial cancer risk were identified based on the administration of combination hormone therapy vs. estrogen only, with combination therapy increasing the likelihood of breast cancer and estrogen only seemingly having no effect. In addition, instead of a reduction in mortality, there was no significant effect on life expectancy among hormone users vs. nonusers. More questions than answers were raised including (a) why were the mortality results of previous cohort studies, e.g., the Nurses' Health Study [15], so different from the results of the WHI randomized trials; (b) why were the outcomes from combination therapy with estrogen plus progestin compared with estrogen only different; and (c) are there differences in the health benefits of hormone therapy for women based on the age or time since menopause when the hormone therapy was started. The only certainty is that controversy remained as to the risks and benefits of different hormone therapy preparations for women of different risk profiles.

20.2 The Present Tense: The Lesson Learned from the WHI

20.2.1 The Role of Personalized Medicine

Several clinical factors, including a women's age, time since menopause, baseline vascular health, risk for breast cancer, biomarker levels, and genetic predisposition, appear to modulate health outcomes on hormone therapy. As a consequence personalized medicine should be applied with special reference to tailoring HT including pharmacodynamics and pharmacokinetics of the different available hormonal

agents because pharmacogenomics is one aspect of personalized medicine that has the potential to impact all areas of medicine, including HT. The goal of pharmacogenomics is to use genetic information to predict how an individual will respond to a drug, with the ultimate objective of aiding clinicians in selecting the right drug, in the right dose, at the right time, for every patient in order to ensure drug efficacy and to avoid adverse drug reactions. Estrogen is the most effective treatment for vasomotor and other symptoms related to menopause, and the current approach to individualizing HT includes consideration of the severity of the menopausal symptoms, a personalized risk assessment, and the patient's personal preferences [16]. Typically, dosing is targeted toward symptom relief, but there is significant variability in the doses required for symptom relief among women. For women experiencing primary ovarian insufficiency (<40 years) or early menopause (<45 years), estrogen therapy is needed not only for symptom management but also protection against the potential long-term adverse health consequences of early estrogen deprivation, including increased risk for cardiovascular disease, osteoporosis, dementia, parkinsonism, mood disorders, sexual dysfunction, and early death [17]. Environmental and biological factors may also impact menopausal symptoms, including body mass index, tobacco, alcohol or caffeine use, stress, anxiety, a history of recent abuse, or adverse childhood experiences [18]. Further work is required to understand the mechanisms by which these environmental and biologic factors affect menopausal symptoms. They may be independent variables or may be intertwined with genetic variation in gene-environment interactions. The strongest factors that have been found to modify CVD risk while taking HT and that appear to help identify better vs. worse candidates for HT use are age, time since menopause onset, LDL cholesterol and other lipid levels, metabolic syndrome, and Factor V Leiden genotype (Table 20.1) [19].

20.2.2 Influence of Age and Time Since Menopause

The WHI analyses reveal that age or time since menopause influences the relation between HT and CHD. In analyses pooling data across both trials, HT-associated RRs for CHD were 0.76 (95% CI 0.50–1.16), 1.10 (95% CI 0.84–1.45), and 1.28 (95% CI 1.03–1.58) among women who were <10, 10–19, and ≥20 years past the menopausal transition at study enrollment, respectively (p, trend = 0.02). Among women aged 50–59, estrogen only was associated with significant reductions in the secondary endpoint of coronary revascularization (RR = 0.55; 95% CI 0.35–0.86) and a composite endpoint of MI, coronary death, or coronary revascularization (RR = 0.66; 95% CI 0.44–0.97), but CHD risk reductions were not seen for ages 60–69 or 70–79. Overall, HT appeared to have a beneficial or neutral effect on CHD in women closer to menopause (who are likely to have healthier arteries) but a harmful effect in later years [20]. In the Early Versus Late Intervention Trial with Estradiol (ELITE), 643 postmenopausal women free from cardiovascular disease were stratified according to time since menopause (<6 years [early] vs. ≥10 years [late]) and were randomly assigned to receive either estrogen such as 17β-estradiol (E2) (plus micronized progesterone vaginal gel for women with a uterus) or placebo

Table 20.1 Selected biomarkers to aid risk stratification for HT decision-making (Adapted from [19])

Biochemical markers:
• Lipids (serum LDL cholesterol, LDL/HDL ratios, triglyceride levels, Lp(a), 27-OH-cholesterol, apolipoprotein levels)
• Inflammatory markers (high-sensitivity C-reactive protein [hsCRP], interleukin-6, tumor necrosis factor alpha, leukocyte count)
• Adipokines (adiponectin, leptin, retinol binding protein-4 [RBP4])
• Endothelial markers (E-selectin, P-selectin, ICAM, VCAM)
• Glucose tolerance markers: fasting glucose, insulin, HOMA-IR, IGF-1, and biomarkers of metabolic syndrome
• Matrix metalloproteinases
• Hemostatic markers (D-dimer, factor VIII, von Willebrand factor, homocysteine, fibrinogen, tissue factor pathway inhibitor or acquired activated protein C resistance)
• Sex steroid hormone levels, sex hormone binding globulin level
Genetic markers:
• Factor V Leiden
• Glycoprotein IIIa leu33pro
• Gene variants in ABO blood group
• Estrogen and progesterone receptor polymorphisms
• Gene variants related to sex hormone biosynthesis
• Gene variants related to sex hormone metabolism
• Gene variants related to sex hormone signaling
• Genome-wide association studies (GWAS) and exome sequencing for gene discovery

over a median of 5 years. The primary outcome was atherosclerosis progression measured by means of ultrasonography such as carotid-artery intima-medial thickness (CIMT). As compared with placebo, estrogen treatment resulted in a significantly lower rate of atherosclerosis progression among early postmenopausal women but not among late postmenopausal women. The results were similar regardless of whether the women also received progesterone [21]. There was no significant difference between estradiol and placebo in either the early or the late postmenopause stratum with regard to a secondary outcome, measurement of atherosclerosis by cardiac computerized tomography (CT) at the end of the study; however, this assessment was performed in only a subset of women, and no baseline measures were available. These data are of keen biologic interest, because they suggest that favorable pharmacodynamic responses of receptors in the vasculature to estrogen may be lost with lack of exposure to estrogen and of note prior to the initiation of the HT, genetic variations in the innate immunity pathway were found to be associated with CIMT and coronary arterial calcification (CAC) [22].

20.2.3 Low Dose Versus High Dose

The primary indication for HT is relief of vasomotor symptoms. Individual risks and benefits should be weighed, and the lowest effective hormone dosage be chosen. For many women, low-dose (<2 mg oral E2/<100 g transdermal E2) or

ultralow-dose HT (<1 mg oral E2/<50 mcg E2) may be sufficient to decrease vasomotor symptoms, but not necessarily to guarantee fracture prevention. Low- and ultralow-dose combined HT has been successfully used in clinical trials but has not been introduced for general use until 2011 [23]. Since then, fixed oral combined ultralow-dose HT containing 17β-E2 has been available as well as patches with varying low-dose 17β-E2. Efficacy and safety were assessed in a 52-week, randomized placebo-controlled trial in 313 postmenopausal healthy women aged 54 years on average. Participants were randomized to (1) 0.5 mg 17β-E2 combined with 2.5 mg dydrogesterone, (2) 1 mg 17β-E2 combined with 5 mg dydrogesterone, or (3) placebo. Both ultralow-dose and low-dose HT significantly reduced moderate to severe vasomotor symptoms [24]. Similarly, the 24-week, randomized, placebo-controlled trial CHOICE demonstrated a significant reduction of vasomotor symptoms by 0.5 mg 17β-E2 combined with either 0.1 mg or 0.25 mg norethindrone acetate (NETA), in 577 postmenopausal healthy women aged 55.5 years on average [25]. Possibly, ultralow-dose HT might be a compromise for those women who are more critical toward HT but in whom alternative and complementary medicine strategies have not been successful. Comparable to standard-dose and low-dose HT, bleeding events may occur when initiating ultralow-dose HT and may require individual dosage adjustments. For women treated with high- or standard-dose HT, switching progressively to low-dose and then to ultralow-dose HT may be a good way to lower hormone dosage without compromising vasomotor symptom relief before stopping HT as soon as it is needed no more. To date, there are no direct head-to-head trials comparing long-term safety of standard-dose, low-dose, and ultralow-dose HT. It appears reasonable to assume that a lower hormone dosage would be associated with fewer estrogenic and especially progestogenic side effects as well as fewer safety concerns, but this has not been conclusively demonstrated. So far, for example, the Nurses' Health Study has demonstrated a lack of increased risk of stroke for ultralow-dose treatment with conjugated estrogens (CEE) [26]. In a nested case-control study based on the United Kingdom's General Practice Research Database, no increased risk of stroke has been observed in users of transdermal HT containing low doses of estrogen, whereas, in users of oral HT, risk was dose-dependent. A more recent review has shown that transdermal estrogens are not associated with a higher risk of recurrent venous thromboembolism among postmenopausal women and that, for oral HT, the dose of estrogens is an important determinant of the thrombotic risk among postmenopausal women using HT [27]. However, until there are clinical studies demonstrating a better long-term safety profile for low-dose or ultralow-dose HT, risks associated with long-term standard-dose HT are most wisely also applicable to ultralow-dose HT despite the biological discrepancies.

20.2.4 Estrogen only Therapy

Looking at the main results from the Heart and Estrogen/progestin Replacement Study (HERS) [28] and the WHI [20], most participants were postmenopausal

American women with at least some degree of comorbidity, and mean participant age in most studies was over 60 years. In relatively healthy postmenopausal women combined continuous HT increased the risk of a coronary event (after 1 year's use: from 2 per 1000 to between 3 and 7 per 1000), venous thromboembolism (after 1 year's use: from 2 per 1000 to between 4 and 11 per 1000), and stroke (after 3 years' use: from 6 per 1000 to between 6 and 12 per 1000). Estrogen only HT increased the risk of venous thromboembolism (after 1–2 years' use: from 2 per 1000 to 2–10 per 1000; after 7 years' use: from 16 per 1000 to 16–28 per 1000), stroke (after 7 years' use: from 24 per 1000 to between 25 and 40 per 1000), but reduced the risk of breast cancer (after 7 years' use: from 25 per 1000 to between 15 and 25 per 1000) and did not increase the risk of coronary events at any follow-up time.

Analysis of the entire follow-up period (i.e., intervention plus post-intervention phases) of the WHI estrogen only trial also found more favorable effects for myocardial infarction (MI) and CHD in younger, compared with older, women. For MI, the RRs associated with randomization to estrogen only were 0.54 (0.34–0.86), 1.05 (0.82–1.35), and 1.23 (0.92–1.65) for ages 50–59, 60–69, and 70–79, respectively (p, interaction = 0.007). Results were similar for CHD [20].

20.2.5 Progestins Not Only One Class

Progesterone and progestogens are nonselective ligands for the progesterone receptor and bind also with other steroid receptors, with agonistic or antagonistic effects according to the structure of the molecule. Their half-life and metabolism are also different, progesterone being rapidly degraded with a short half-life. Progestogen compounds of combined estrogen-progestogen therapy include both progesterone (the bioidentical compound synthesized and secreted by the ovary) and synthetic compounds named progestins, which are derived from either progesterone (pregnanes and 19-norpregnanes) or testosterone (19-nortestosterone). Pregnane derivatives consist of different molecules, including dydrogesterone, medrogestone, chlormadinone acetate, cyproterone acetate, and medroxyprogesterone acetate (MPA). Norpregnane derivatives include nomegestrol acetate, promegestone, trimegestone, and nestorone. Finally, nortestosterone derivatives consist of ethinylated derivatives, nonethinylated derivatives, spironolactone derivatives, and tibolone. Nortestosterone ethinylated derivatives are composed of estranes (including especially norethisterone acetate) and gonanes, which are preferentially used in contraceptive pills. Nortestosterone nonethinylated derivative (dienogest) and spironolactone derivative (drospirenone) are also used in contraception.

As an HT compound, progestogens are always combined with estrogens and are almost exclusively administered by the oral route. However, across countries, medical practices regarding HT use may present important differences in terms of chemical structure and route of administration. In France, women are preferentially prescribed transdermally administered 17β-E2 combined with micronized progesterone. By contrast, oral CEE combined with MPA are often used in the United States.

20.2.6 Differential Effects of Progestogens on Thrombosis Risk

As progestogens consist of several compounds with different pharmacologic properties and all, when added to estrogens for women with an intact uterus, reduce the increased risks of endometrial hyperplasia and cancer, randomized controlled trials that are able to assess the main effects of a progestogen or to compare different progestogens are scarce. In the PEPI (Postmenopausal Estrogen/Progestin Interventions) trial, MPA was administered either sequentially or continuously, and these two hormone regimens were compared with micronized progesterone or no progestogen. Results showed similar changes in fibrinogen across different active groups, with neither an effect of addition of a progestogen nor a specific effect of different chemical structures [29]. A few years later, Lobo et al. [30] conducted a large trial with different doses of CEE alone or combined with MPA and did not highlight any evidence for a specific effect of MPA on hemostatic parameters. At the same time, van Baal et al. [31] and Post et al. [32, 33] investigated the impact of dydrogesterone and trimegestone, a pregnane and a norpregnane derivative, respectively. Here, they also found no difference in their effects on hemostasis and pooled the two groups receiving opposed oral estrogens for some specific analyses. In another study, the main effect of gestodene, a testosterone derivative, was assessed by comparing changes in hemostatic parameters between two arms consisting of oral estrogens either alone or combined with this progestin [34]. This was the only study that found a decrease in protein C in the opposed oral estrogen group but not in the estrogen only group.

Overall, randomized controlled trials did not consistently detect any specific effect of progestogen on hemostasis among postmenopausal women using oral estrogens. Nevertheless, this absence of association does not necessarily imply that progestogens have no effect. It could be partly explained by a lack of statistical power and/or a dilution effect caused by the concomitant use of oral estrogens that activate blood coagulation by themselves and might then hide the specific effect of progestogens. A cross-sectional study on postmenopausal HT and hemostasis suggested that norpregnane derivatives and micronized progesterone could have a differential effect on APC resistance and blood coagulation activation when combined with transdermal estrogens [35]. In addition, clinical data support a differential effect of pharmacologic classes of progestogens on thrombotic risk [36, 37]. Further data on the biological and clinical effects of progestogens are therefore needed, especially in the context of transdermal estrogen use.

20.2.7 Oral Versus Non-oral Administration Forms

As already pointed out, estrogen dose and routes of administration vary in regard to their risks. Lower doses are associated with less adverse effects like breast tenderness or uterine bleeding and may have a more favorable risk-benefit ratio than standard doses. Transdermal estrogen is preferred to the oral route, as the latter is subject to first-pass hepatic metabolism which promotes prothrombotic hemostatic changes in

factor IX, activated protein C resistance, and tissue-plasminogen activator [38]. Furthermore, observational data from the Estrogen and Thromboembolism Risk (ESTHER) multicenter case-control study of thromboembolism among postmenopausal women demonstrated an odds ratio for venous thromboembolism in users of oral estrogen to be 4.2 (95% CI, 1.5–11.6) and 0.9 (95% CI, 0.4–2.1) for transdermal estrogen, compared to nonusers [36]. In accordance, 22 studies were included in meta-analyses (nine case-control studies, nine cohort studies, and four randomized controlled trials). As compared to control groups, VTE risk was not increased with non-oral HT, including users of estrogens and estrogens plus progestins (OR 0.97 [0.9–1.06]), non-oral estrogen therapy (ET)-only (OR 0.95 [0.81–1.10]), and non-oral combined estrogen-progestin therapy (OR 0.92 [0.77–1.09]). Conversely, increased risk of VTE was observed as compared with control groups in users of oral HT, including users of estrogens and estrogens plus progestins HT (OR 1.72 [1.47–2.01]), oral ET-only (OR 1.43 [1.34–1.53]), and combined oral estrogen-progestin HT (OR 2.35 [1.9–2.9]). The comparison of non-oral vs. oral HT showed increased VTE risk with oral HT (OR 1.66 [1.39–1.98]) [39]. The authors consider the quality of the evidence produced in their meta-analyses which is low to moderate, and further clinical trials are needed to sort out the impact of different types of progestin and different estrogen doses and administration routes on VTE risk. However, this approach has been endorsed by the American College of Obstetricians and Gynecologists, as gynecologists were recommended to take into consideration the possible thrombosis-sparing properties of transdermal forms of estrogen therapy [40].

20.3 Conclusion

Ideally, HT should be initiated in the perimenopause or early postmenopause, but not 10 or more years after menopause as atherosclerotic changes are likely to have occurred by then, increasing, for example, the risk of myocardial infarction. However, the choice of a particular modality should be guided by the patient's risk profile, other symptoms, and preferences considered for each patient during the decision-making. We have to date wider repertoire of agents for successful treatment than ever. This report has focused on vascular health and reviewed the evidence on the role of pharmacology and pharmacogenomics in tailoring the use of hormone therapy to appropriate candidates in order to develop a personalized risk-benefit prediction model that takes into account clinical and genetic factors. The proposed personalized approach to HT decision-making has also the potential to improve the quality of health care including also "patient-centered" outcomes such as sense of well-being and quality of life. However, due to the complexity of both the estrogen pharmacodynamic and pharmacokinetic pathways, and the many additional variables reviewed here that may be of importance, large studies will be required to develop genetically based algorithms for estrogen administration/dosing.

US Preventive services Task Force (USPSTF) process. The introduction of continuous combined ultra-low-dose MHT enlarge our possibilities to individualize the

treatment of symptomatic postmenopausal women. Thus, the risk can be avoided of serum hormone fluctuations arising from the previous practice of splitting tablets or cutting patches to reduce the hormone dosage of low-dose MHT.

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