

PERSONAL PERSPECTIVE

A theory of eu-estrogenemia: a unifying concept

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Abstract

Objective: The aim of the study was to propose a unifying theory for the role of estrogen in postmenopausal women through examples in basic science, randomized controlled trials, observational studies, and clinical practice.

Methods: Review and evaluation of the literature relating to estrogen.

Discussion: The role of hormone therapy and ubiquitous estrogen receptors after reproductive senescence gains insight from basic science models. Observational studies and individualized patient care in clinical practice may show outcomes that are not reproduced in randomized clinical trials. The understanding gained from the *timing hypothesis* for atherosclerosis, the *critical window theory* in neurosciences, randomized controlled trials, and numerous genomic and nongenomic actions of estrogen discovered in basic science provides new explanations to clinical challenges that practitioners face. Consequences of a hypo-estrogenemic duration in women's lives are poorly understood. The Study of Women Across the Nation suggests its magnitude is greater than was previously acknowledged. We propose that the healthy user bias was the result of surgical treatment (hysterectomy with oophorectomy) for many gynecological maladies followed by pharmacological and physiological doses of estrogen to optimize patient quality of life. The past decade of research has begun to demonstrate the role of estrogen in homeostasis.

Conclusions: The theory of eu-estrogenemia provides a robust framework to unify the timing hypothesis, critical window theory, randomized controlled trials, the basic science of estrogen receptors, and clinical observations of patients over the past five decades.

Key Words: Critical Window Theory – Eu-estrogenemia – Healthy user bias – Hormone therapy – Timing Hypothesis – Women's Health Initiative.

Estrogen is the best known and the most controversial hormone discussed in medical and lay literature. Over the past 70+ years, the use of estrogen has waxed and waned so often that both patients and medical professionals continue to be confused about the risks and benefits of estrogen administration. The conclusions of the older observational studies from the 1980s and 1990s have been partially discredited.¹ More recent randomized control trials (RCTs) such as the Heart and Estrogen/Progestin Replacement Study

(HERS),² Women's Health Initiative (WHI),³ Kronos Early Estrogen Prevention Study (KEEPS),⁴ and Early versus Late Intervention Trial of Estradiol (ELITE),⁵ newer observational studies, for example, Study of Women Across the Nation (SWAN),⁶ and animal studies (cynomolgus monkeys by Clarkson et al⁷⁻¹⁰ including JR Kaplan, CA Shively, Thomas Register, KP Klein, MS Anthony, TS Mikkola et al) have changed the paradigm of estrogen administration for the hypo-estrogenemic woman. In this personal perspective, we attempt to clarify the data and present a unifying concept which we call eu-estrogenemia (Eu-E)¹¹—the true and good concentration of estrogen at which more than 3,600 ubiquitous estrogen receptors (ERs)¹² function optimally and continuously.

Historically, Wilson and Wilson¹³ advocated estrogen forever to keep women young and vibrant. Subsequently, estrogen was promoted to decrease osteoporosis and heart disease. Currently, the US Food and Drug Administration (FDA) recommendations are to treat only vasomotor symptoms (VMS) and genitourinary syndrome of menopause (GSM), and possibly to prevent progression of osteopenia to osteoporosis with the lowest dose for the shortest duration of time. We question whether it is "normal" for these ubiquitous receptors to perform suboptimally in the postreproductive phase of a woman's life and ignore all of the other putative benefits of

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estrogen. If menopause is physiological and a natural concomitant of aging as espoused by many, then why do we treat hypo-estrogenemic conditions such as VMS, GSM, and osteoporosis?

The *timing hypothesis*⁷ and *critical window theory*¹⁴ have been proposed to explain that the ER response is variable and time-related. That is, the receptors appear to respond to estrogen if administered early after a brief period of absence, but may not respond to late administration. This concept has been validated by cynomolgus monkey studies by Clarkson et al,⁷⁻¹⁰ Suzuki et al's¹⁵ rodent studies, and the WHI³ and Heart and Estrogen/progestin Replacement Study (HERS).² After an organ-specific duration of hypo-estrogenemia, ERs do not respond as they previously functioned. We call this period of ER nonresponsiveness, the geripause, indicating that "re-estrogenization" is not always possible.¹⁶

Let us consider the quality of a woman's life in relation to the function of her ovaries. Figure 1 shows the changing estrogenic milieu throughout a woman's life.¹⁶⁻¹⁸ She is pre-estrogenic before menarche and eu-estrogenemic after menarche. She becomes hyperestrogenemic during pregnancy, with dramatic changes in estrogen concentration and function. Reproductive senescence or ovarian failure brings the onset of the hypo-estrogenemic milieu. Hormone therapy (HT) in early menopause may restore receptor function in many organ systems. Late administration of HT, as seen in WHI and HERS ("re-estrogenization"), may not result in restoration of the ER function—"geripause." Because estradiol (E₂) concentration gradually declines through the woman's reproductive years, the theory of eu-estrogenemia advocates estrogen therapy (ET) to maintain optimal ER function—Eu-E (represented by the dotted line in the graph of Fig. 1).

Vasomotor symptoms may begin up to 7 years before the final menses and may last 7 years after the final menses.⁶ The jagged line depicting erratic and declining E₂ concentration

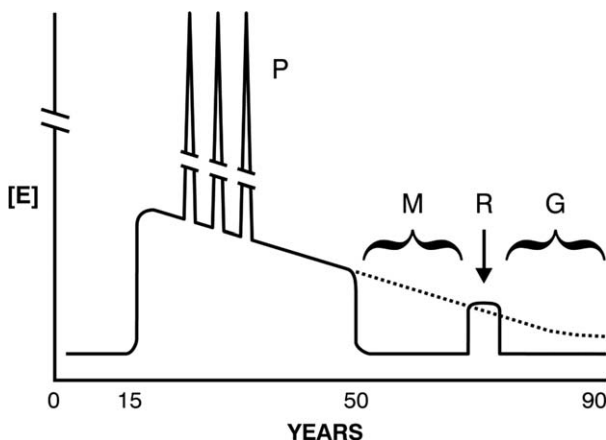


FIG. 1. The abscissa (*x* axis) shows the woman's age in years. The ordinate (*y* axis) shows [E], the concentration of estrogen in cell and the bloodstream. The dotted line represents the concept of eu-estrogenemia, that is, the concentration of estrogen in cells and the blood stream at which all estrogen receptors function optimally. P, pregnancies; M, menopause; R = re-estrogenization; G, geripause. Reprinted from Turner and Kerber¹⁷ with permission of the publisher. Copyright © 2008, International Urogynecological Association.

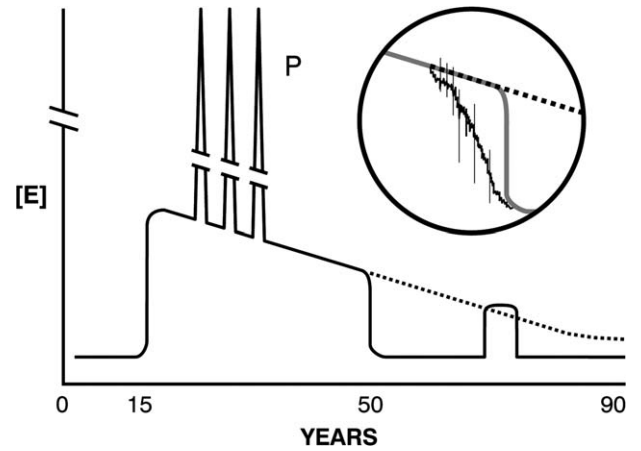


FIG. 2. The abscissa (*x* axis) shows the woman's age in years. The ordinate (*y* axis) shows [E], the concentration of estrogen in the cell and the bloodstream. The dotted line represents the concept of "eu-estrogenemia," that is, the concentration of estrogen in cells and the blood stream at which all estrogen receptors functions optimally. The inset shows ovulatory dysfunction in the menopausal transition. P = pregnancies. Reprinted from Turner and Kerber¹⁸ with permission of the publisher. Copyright © 2011, North American Menopause Society.

(Fig. 2) illustrates the hypothalamically mediated ovulatory dysfunction studied by Clarkson et al,⁷⁻⁹ and as manifested in the menopausal transition of the SWAN.⁶ Mittelman-Smith et al¹⁹ showed that VMS arise in the ERs co-expressed in the Kisspeptin/Neurotrophin B/Dynorphin (KNDy) neurons in the arcuate nucleus in the brain. We interpret these findings that VMS are manifestations of ovulatory dysfunction/hypo-estrogenemia detected in the ERs in the KNDy neurons. VMS become the "canary in the coal mine," signaling estrogen production has begun to fluctuate.²⁰

The theory of eu-estrogenemia explains the variations in estrogen function at the different stages of a woman's life. Likewise, the ubiquitous nature of ER in women and men, and the systemic implications of proper ER function lead us to the paradigm shift of estrogen as a hormone of homeostasis. We believe that Figures 1 and 2 unify the concepts. We will interpret the literature in the light of these two graphs.

THE TIMING HYPOTHESIS AND EU-ESTROGENEMIA

Clarkson et al studied cynomolgous female monkeys and showed atherosclerosis could be prevented by estrogen administration in oophorectomized monkeys if given within 2 years of castration (equivalent to 6 human years), but failed to protect the monkeys if given more than 2 years after castration. Clarkson et al also studied ER function in nondominant, hypothalamically stressed females with ovulatory dysfunction and hypo-estrogenemia. These monkeys had decreased follicular-phase plasma E₂ concentrations (<80 pg/mL in stressed, nondominant study monkeys vs ~240 pg/mL in dominant nonstressed controls), increased risk for central obesity, lower high-density lipoprotein (HDL) concentrations (28 mg/dL in stressed monkeys vs 48 mg/dL in dominant controls), an abnormal vasoconstrictive

arterial response to acetylcholine administration, and increased plaque area of coronary atherosclerosis (0.225 mm^2 atherosclerotic plaque area vs 0.030 mm^2 for nonstressed controls).⁷⁻⁹ He concluded: "Estrogen effects on arteries vary with stage of reproductive life and extent of subclinical atherosclerosis progression."⁷ From the perspective of the Theory, these data substantiate the ovulatory dysfunction manifested by erratic estrogen production in the menopause transition as illustrated in the inset of Figure 2.

Bairey Merz et al,²¹ in the Women's Ischemia Syndrome Evaluation (WISE) study, showed that premenopausal women with angiographic coronary artery disease (CAD) ($n=13$) had significantly lower E_2 , bioavailable E_2 , and follicle-stimulating hormone (FSH) (all $P < 0.05$) than women without angiographic CAD ($n=82$), even after controlling for age. Hypoestrogenemia of hypothalamic origin was the most powerful predictor of angiographic CAD in a multivariate model (odds ratio [OR] 7.4, confidence interval [CI] 1.7-33.3, $P=0.008$). Women who had taken oral contraceptives (OCs) had less severe coronary artery severity scores, assessed by quantitative coronary angiography, than nonusers ($n=408$). Past OC users ($n=264$) had coronary severity scores of 11.8 ± 10.3 versus 18.7 ± 17.3 for nonusers ($n=408$; $P=0.002$).²² Eu-E can explain both findings.

THE CRITICAL WINDOW THEORY AND EU-ESTROGENEMIA

Studies in mice by Suzuki et al¹⁵ also demonstrate the critical window theory in the nervous system. They studied four groups of oophorectomized mice comparing the four permutations of early or late administration of ET or placebo on brain infarct after middle cerebral artery occlusion. The mice with continuous exposure to E_2 (Eu-E) had reduced volume of infarcted brain tissue after middle cerebral artery occlusion, when compared with interrupted or late administration of E_2 or with placebo in oophorectomized mice. Likewise, the mice with Eu-E received neuro-protection with less total infarct volume, less injury to cortex, and less injury to striatum. They concluded that E_2 protected the brain tissue by suppressing the inflammation through ER α -mediated mechanisms. E_2 down-regulates the expression of proinflammatory cytokines, including interleukin (IL)-6, monocyte chemoattractant protein 1 (MCP-1), and tumor necrosis factor (TNF)- α . They also concluded the timing of ET after ovariectomy dictated the efficacy of its neuroprotective and anti-inflammatory actions, thus the critical window theory. Restating the critical window theory according to the theory of eu-estrogenemia, mice with continuous administration of E_2 after oophorectomy, for example, continuous "eu-estrogenemia," had the least damage due to the physiological action of estrogen.

Concerning stroke and the neuroprotective effects of estrogen, Dubal and Wise²³ have stated "women may now live over three decades of their lives in a hypoestrogenic, postmenopausal state. The impact of prolonged hypoestrogenicity is now a critical health concern... conversely

replacement with estrogen appears to act in the primary prevention of many disease processes, including neurodegeneration." Furthermore, Dubal and Wise postulated that pharmacologic levels of E_2 protect through mechanisms that do not require ERs, whereas physiological levels of E_2 protect the brain through mechanisms that depend on ERs. Marder and Sano²⁴ stated that the precipitous depletion of endogenous estrogens at menopause may have the greatest deleterious effect on neurons.

THE ROLE OF MITOCHONDRIA IN ESTROGEN-INDUCED NEUROPROTECTION

The review article by Simpkins et al²⁵ maintains that mitochondria play a central role in estrogen-induced neuroprotection. Estrogens prevent cell death by maintaining functionally intact mitochondria.²⁵ Estrogen is protective against various oxidative stress insults by multiple mechanisms in mitochondria including preserving adenosine triphosphate (ATP) function, preventing production of reactive oxygen species (ROS), resisting cellular and mitochondrial Ca^{+2} loading, and preserving mitochondrial membrane potential during insults. Brinton's laboratory has corroborated findings by Hoyer²⁶ that mitochondria burn glucose over alternative fuels (ketones) 100:1 in the presence of normal estrogen in young controls. Clinical observations of patients with incipient Alzheimer's disease (AD) show that ratio of utilization of glucose to ketones is 2:1, whereas comparably matched aged controls show a ratio of 29:1. After menopause and not on HT, estrogen levels are low. ERs do not function effectively. There is a concomitant decline in ATP generation. Instead, mitochondria use ketones, the breakdown product of which is beta-amyloid. Brinton's research into mitochondrial bioenergetics suggests that some phenotypes might benefit from estrogen administration during an optimal time window during perimenopause/reproductive senescence.^{27,28}

However, estrogen has age-related pleiotropic effects on mitochondria. In the young, estrogen increases mitochondrial electron transport and prevents dysfunction; for example, ATP depletion and reduced membrane potential.²⁹ Reproductive senescence (hypoestrogenemia) markedly exacerbates mitochondrial dysfunction. Mitochondrial dysfunction provides a plausible mechanistic rationale for the hypometabolism in the brain that precedes AD diagnoses and suggests therapeutic targets for prevention of AD.

An interesting study on duration of AD is the Cache County Utah prospective study.³⁰ Prior HT use decreased the risk of AD, but there was no benefit to current users unless there was more than 10 years of HT use (Fig. 3). Ten years of postmenopausal HT use for women mimics the AD risk for men. We surmise that aromatization of testosterone in men in later life was sufficient to postpone AD. Likewise, more than 10 years' HT use by women in menopause extends the duration of eu-estrogenemia to preserve mitochondrial function and decreases the risk of AD. In the aged and women beyond the critical window, the accumulation of senescent cells with proinflammatory processes may counter normal

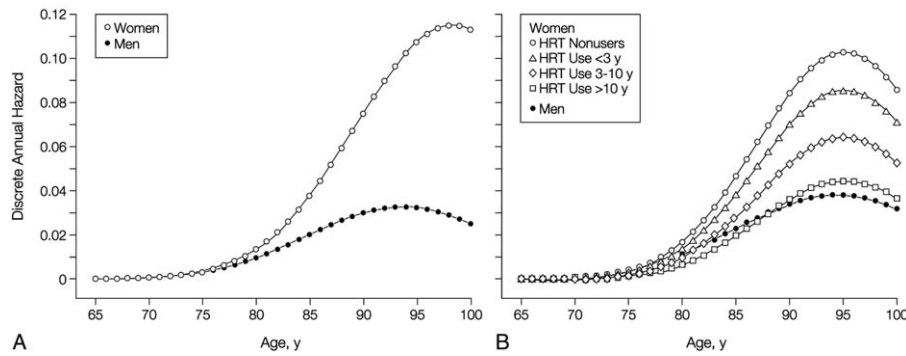


FIG. 3. Estimated discrete annual hazard of Alzheimer's disease (AD) for men and women by age, and by duration of hormone therapy (HT) use for women. Both figures indicate risks estimated for an individual with the mean value of 13 years of education and no $\epsilon 4$ alleles at apolipoprotein E. (A) The curves depict the annual hazards predicted by fitting the base model including an age-by-sex interaction term. The annual hazard for AD appears similar for men and women before 80 years of age, but diverges rapidly afterward with an excess risk found in women. (B) The curves depict the annual hazards predicted for the women with available HT exposure information, and, in filled circles, the corresponding annual hazards for men after omitting the terms for HT. There were 35 instances of incident AD among 1,357 men. Ordinate values for women differ slightly from those in panel A due to omission of women lacking HT exposure information, several of whom experienced incident dementia. Reprinted from Zandi et al³⁰ with permission of the publisher. Copyright © 2002, American Medical Association.

estrogen response to estrogen and ET.²⁹ This pleiotropic effect suggests that maintaining healthy mitochondria, Eu-E, is a physiological goal. In terms of the theory, one cannot “re-estrogenize” senescent mitochondria. This finding is consistent with The Women's Health Initiative Memory Study, which showed no benefit and possible deleterious effects when HT was started in women aged 65 to 79 years.³¹

CARDIOVASCULAR SYSTEMS AND EU-ESTROGENEMIA

Kronos Early Estrogen Prevention Study (KEEPS)³ and ELITE⁴ have evaluated the timing hypothesis. KEEPS involved 727 participants randomized to three groups, two formulations of HT, oral 0.45 mg conjugated equine estrogen (o-CEE), or 0.05 mg transdermal patch administered weekly (t-E₂), and a placebo group. The progestin was 200 mg of micronized oral progesterone for 12 days each month, instead of a daily oral dose of 2.5 mg of medroxyprogesterone acetate in the WHI. It should be taken into account that the o-CEE dose of 0.45 mg was less than the 0.625 mg dose in the WHI. To assess the progression of atherosclerosis, researchers in KEEPS conducted yearly measurements of carotid intima media thickness (CIMT) on all participants. Coronary artery calcium (CAC—a marker for atherosclerotic plaque) was also assessed using high-resolution computer assisted tomography scans before and at the end of the study. There were similar rates of progression of arterial wall thickness in all three treatment groups over the 4-year study period. These changes were generally small, limiting the statistical power to detect any differences among the groups. Despite these small numbers, there was a trend toward less progression of CAC in the two HT groups.⁴

The ELITE enrolled 643 healthy postmenopausal women who were stratified according to time since menopause (<6 years [early postmenopause] or ≥ 10 years [late postmenopause]) in a two-by-two RCT.⁵ These women were

randomly assigned to receive either oral 17 β -E₂ (1 mg/d, plus progesterone [45 mg] vaginal gel administered sequentially [ie, once daily for 10 days of each 30-day cycle] for women with a uterus) or placebo (plus sequential placebo vaginal gel for women without a uterus). The primary outcome was the rate of change in CIMT, which was measured every 6 months. Secondary outcomes included an assessment of coronary atherosclerosis by cardiac computed tomography (CT), which was performed when participants completed the randomly assigned regimen. After a median of 5 years, the effect of E₂, with or without progesterone, the early postmenopause women showed on CIMT progression, 0.0078 mm/y in the placebo group versus 0.0044 mm/y in the E₂ group ($P=0.008$). Among women who were 10 or more years past menopause at the time of randomization, the rates of CIMT progression in the placebo and E₂ groups were similar (0.0088 and 0.0100 mm/y, respectively; $P=0.29$), which would demonstrate the timing hypothesis and confirm the Theory that one cannot “re-estrogenize” a patient. CT measures of CAC, total stenosis, and plaque did not differ significantly between the placebo group and the E₂ group in either of the postmenopausal stratum. E₂ had no significant effect on cardiac CT measures of atherosclerosis in either of the postmenopausal stratum. According to the Theory, one could postulate the lack of response to E₂, even within 6 years of menopause (dating 12 months after the last menstrual period), is too late, because the ER-associated systems in healthy endothelium have been sufficiently down-regulated by this time to halt the damage. Vasomotor instability begins before the defined onset of menopause,⁶ and might be the critical time for the healthily functioning or dysfunctioning endothelium (suggested in Fig. 2). This prompts us to consider ET for Eu-E earlier in the woman's life.

MENOPAUSAL HOT FLASHES AND CIMT

Thurston et al evaluated 295 nonsmoking late perimenopausal and menopausal women free of cardiovascular disease

(CVD), who underwent ambulatory physiologic hot flash assessment, a blood draw, and carotid ultrasound measurement of intima media thickness and atherosclerotic plaque. The women were aged 40 to 60 years. Half of them reported VMS (flashers) and the other half did not (nonflashers). Flashers reported five episodes every 24 hours, but 12 physiological events were detected. Among nonflashers, physiological episodes were detected at low frequency (0-5/24 h, interquartile range). More frequent physiologic hot flashes were associated with higher CIMT for each additional hot flash ($P=0.0001$), reported hot flash ($P=0.002$), and plaque index relative to no plaque ($P=0.04$). They concluded that “among women reporting daily hot flashes, frequent hot flashes may provide information about a woman’s vascular status beyond standard CVD risk factors and serum E_2 . Frequent hot flashes may mark a vulnerable vascular phenotype among midlife women”.³² Interpreting these findings in light of the Theory, we postulate that hypoestrogenemia in the midlife transition is similar to Clarkson et al’s hypothalamically mediated ovulatory dysfunction (seen in Fig. 2), manifested as endothelial dysfunction. Pharmacologic treatment might restore Eu-E and healthy endothelium.

CARDIOVASCULAR SYSTEMS

In cardiovascular systems, there are several distinct mechanisms of action by ERs. Tarhouni et al³³ studied flow (shear stress)-mediated outward remodeling (FMR) of resistance arteries, which is a key adaptive process, allowing collateral growth after arterial occlusion, but which declines with age. Estrogen, specifically E_2 , has a key role in the process through activation of ERs. Prolonged E_2 deprivation induced a loss of the ability of E_2 to restore remodeling and was associated with reduced ER α and endogenous nitric oxide synthase (eNOS) expression. Tarhouni et al concluded that E_2 deprivation, rather than age, leads to a decline in FMR, which can be prevented by early exogenous E_2 . However, delayed E_2 replacement was ineffective on FMR, underlining the importance of timing of this estrogen action. Tarhouni et al also considered the action of ER α activity in FMR to be a possible contributor to the timing hypothesis.

Barrett-Muller et al³⁴ employed a new model for E_2 and ER. E_2 -activated ER in endothelial cells forms a complex with mineralocorticoid receptor (MR) in the nucleus to modulate MR regulation of the inflammatory glycoprotein, intracellular adhesion molecule-1 (ICAM1). The authors state E_2 inhibition of MR regulation of genes that contribute to CVD may be a new mechanism by which premenopausal women are protected from CVD.³⁴

The study by Barrett-Muller et al reminds us that the pharmacokinetics of ERs are robust. Umetani et al³⁵ show that 27-hydroxycholesterol (27HC), an abundant cholesterol metabolite that is elevated with hypercholesterolemia and found in atherosclerotic lesions, is a competitive inhibitor of ER action in the vasculature. An aspect of the Theory is to understand the actions of selective estrogen receptor modulators (SERMs) and ERs. Therefore, 27HC functions as an

endogenous SERM that inhibits the cardiovascular effects of estrogen. Umetani et al³⁶ have also shown that 27HC promotes atherosclerosis via novel proinflammatory processes mediated by ER α , and it attenuates estrogen-related atheroprotection. He proposes that strategies to lower 27HC may complement approaches to targeting cholesterol to prevent vascular disease. These complex actions in the cell involving ER are concordant with the Theory and the concern for proper and beneficial ER function. Exogenous E_2 administration could counteract the deleterious actions of 27HC on a pharmacokinetic basis. This would explain the beneficial effects of exogenous E_2 , (50 mcg oral ethinyl estradiol), administered to Clarkson et al’s stressed monkeys experiencing hypothalamically mediated ovulatory dysfunction.⁹

RETINA, EYE DISEASE, AND EU-ESTROGENEMIA

A clinical trial of vascular function in the retina was performed by Deschênes et al.³⁷ Her group evaluated retinal artery blood flow in 35 postmenopausal HT continuous users versus 29 postmenopausal never-users.³⁷ The HT women showed long-term use effects including increased retinal tissue perfusion via blood flow through the infero-temporal retinal artery ($P=0.0006$), greater rim volume for the entire optic nerve head (ONH) region ($P=0.032$), and greater rim volume ($P=0.042$), height variation contour ($P=0.011$), mean thickness ($P=0.033$), and cross-sectional area ($P=0.020$) of the retinal nerve fiber layer for the infero-temporal region of the ONH. The authors corroborated their clinical findings in a rat oophorectomy plus E_2 model, which showed increased retinal tissue perfusion in the range of 22% to 45% in the E_2 treatment group. Deschênes et al³⁸ expressed concern for women in the hypoestrogenic state, for example, “early menopause onset, premature ovarian failure caused by chemotherapy and radiotherapy, genetic disorders, hypopituitarism, and in women undergoing aromatase inhibitor or selective ER modulator therapy for treating or preventing the recurrence of breast cancer.” They also expressed concern for age-related macular degeneration and glaucoma arising from the hypo-estrogenic state.³⁸

The Eye Disease Case Control Study Group at the National Eye Institute showed decreased risk of age-related (wet) macular degeneration with postmenopausal exogenous estrogen use.³⁹ The Beaver Dam Eye Study, a prevalence survey study of eye-related disease in a community, found a modest protective effect of long-term estrogen use on lens opacities with at least 5 years use and the greatest benefit with 20 years of postmenopausal hormone use (OR 0.65, 95% CI 0.48-0.90).⁴⁰

Fluorophotometry is not routinely used as a clinical assessment by ophthalmologists in the United States. However, in a case-controlled study using fluorophotometry in Spanish women and men in their mid to late 40s, lens transmittance values were obtained. Nineteen postmenopausal estrogen users (group 1) were aged 46.3 ± 4.4 years with menopause at 43.4 ± 3.1 years. Twenty postmenopausal nonusers (group 2) were aged 47.4 ± 3.7 years with menopause at

42.4 years \pm 2.7 years. Twenty-three men (group 3) served as controls. Their age was 47.8 ± 6.9 years. Lens transmittance values for the three groups, respectively, were 0.905 ± 0.03 , 0.839 ± 0.08 , and 0.841 ± 0.08 . The differences in lens transmittance between group 1 (women with HT) and the other two groups were statistically significant ($P = 0.01$). The authors concluded that these data are suggestive of a protective effect of estrogen use on the lenses of postmenopausal women.⁴¹ According to the Theory, the “eu-estrogenemic” women on HT had better values for light transmittance.

SKIN AND EU-ESTROGENEMIA

The benefit of estrogen is seen in the mouse skin flap model. The protective effect of E_2 was demonstrated in ovariectomized mice. Necrosis was involved in the half portion of the skin flap within 1 week of surgery, but was reduced 10-fold when pretreated for at least 3 days before the surgery. Benefits included protection of the vascular network and facilitated reperfusion. There was increased expression of fibroblast growth factor-2 (FGF-2) isoforms and circulating vascular endothelial growth factor (VEGF) in the serum. The protective effect was abolished in ER α -deficient mice, but was found to be mimicked by the SERM tamoxifen.⁴²

Raine-Fenning et al⁴³ reviewed the impact of estrogen on skin in menopause. ER function and dermal cellular metabolism are influenced by hypoestrogenemia, leading to changes in collagen content, and alterations in concentration of glycoaminoglycans and water content. Skin turgor and capillary blood flow velocity are significantly decreased in menopause, but are reversible with HT.⁴³

THE ROLE OF EU-ESTROGENEMIA IN LIVER FUNCTION, DIABETES, AND METABOLISM

The ovariectomized (OVX) mouse model gives us insight into ER function in the liver. For women who cannot or will not take estrogen, exercise may offer effective options to prevent metabolic dysfunction. However, in ovariectomized mouse models, Spangenberg et al⁴⁴ found that exogenous E_2 replacement corrects lipolytic dysregulation that is not achieved using the exercise wheel. Spangenberg states, “estrogens encourage physiological mechanisms that prevent chronic disease.” Furthermore, there is a clear association of lost estrogen function with the onset of metabolic disease. Because exogenous delivery of 17β - E_2 can prevent or reverse metabolic dysfunction in OVX or aromatase knockout mice (ARKO), these kinesiologists call estrogen “the critical regulator of metabolism and not another ovarian hormone.” Estrogen appears protective in nonalcoholic fatty liver disease. Conversely, reduced circulating estrogens result in adipocyte hypertrophy and change in lipid metabolism in the liver.⁴⁴ These metabolic changes, including increased visceral fat, are consistent with findings in Clarkson et al’s⁹ stressed monkeys.

Pereira et al⁴⁵ considered the timing of E_2 treatment after menopause to determine benefit or harm to insulin action. The group studied the insulin-mediated glucose disposal rate

(GDR) in 46 HT-naïve postmenopausal women. The early postmenopausal (EPM) group of 22 was less than 6 years from onset of menopause or bilateral oophorectomy. The late postmenopausal (LPM) group of 24 was more than 10 years from menopause or bilateral oophorectomy. The intervention compared 1 week of transdermal E_2 (0.15 mg; three 0.05 mg patches) and placebo crossover in a two-stage (4 and 40 mU/m²/min), 3.5-hour hyperinsulinemic-euglycemic clamp. E_2 administration appeared to increase GDR in EPM women (benefit) and decrease GDR in LPM women (harm). They stated, “These data suggest that the physiologic effect of E_2 on glucoregulatory insulin action (glucose disposal) depends on the timing of treatment relative to menopause.”⁴⁵

Maalouf et al⁴⁶ analyzed the WHI database for kidney stones. We examined Maalouf et al’s presentation of the data for the timing hypothesis and found that only the cohorts of women 6 to 10 years beyond the menopause and aged 60 to 64 had CIs of hazard ratio (HR) greater than 1 (Figs. 4 and 5). We proposed the geripause effect on kidney stone formation around small atherosclerotic niduses in the renal pelvis, that is, estrogen administration in women 6 to 10 years postmenopausal or aged 60 to 64 were at increased risk of kidney stone formation.¹⁸ The serendipitous discovery of the timing hypothesis appearing in the WHI database for renal stones corroborated the Theory. An expanded review of the WHI health records for other disease processes that reflect the timing hypothesis manifested in other organ systems may give other insights into ER function.

EU-ESTROGENEMIA AND MENTAL ILLNESS

In dealing with human variables, large numbers of studies are required for meta-analysis. To evaluate estrogen and menopausal depression, Georgakis et al⁴⁷ recently performed meta-analysis of 67,714 women in 14 studies. They found an inverse relationship for postmenopausal depression with increasing age at menopause (OR 0.98, 95% CI of 2-year increments 0.96-0.99) and duration of reproductive period (OR 0.98, 95% CI of 2-year increments 0.96-0.99). The longer exposure to endogenous estrogens, expressed as older age at menopause and longer reproductive period, was associated with a lower risk of depression in later life. In the accompanying editorial, Joffe and Bromberger⁴⁸ noted that estrogen improves mood in depressed premenopausal women, but not postmenopausal women, concluding depression in postmenopausal women is not hormonally sensitive. Georgakis et al stated that ERs in postmenopausal women are no longer responsive to estrogen. In evaluating these data, is this not psychiatrists restating eu-estrogenemia and a Critical Window Theory for psychiatry? These are consistent with the theory of eu-estrogenemia.

OSTEOPOROSIS AND EU-ESTROGENEMIA

Considering osteoporosis, after the release of the WHI in 2002, Islam et al⁴⁹ reviewed an insurance database of women 40 to 69 years of age from 2003 to 2005. There was an increase in fractures in all categories: radius, ulna, vertebra, hip, pelvis, multiple, and pathologic ($P = 0.03$). Women who

stopped HT (ET or estrogen and progestin therapy) did not begin alternate therapies.⁴⁹

OBSERVATIONAL STUDIES OF STROKE AND HT

Several studies were conducted on the Leisure World cohort in Laguna Beach—a white, affluent, well-educated community that was created in 1981. The HT users in this cohort usually had the onset of HT administration during the menopausal transition or onset of surgical menopause, received varying doses of estrogen formulations or cyclic regimens of HT, and were clinically monitored for quality of life. Use of HT was decades in duration. Paganini-Hill et al⁵⁰ evaluated mortality from stroke. Twenty of 4,962 users who used estrogen replacement died from stroke compared with 43 out of 3,845 nonusers (risk ratio [RR] 0.53, 95% CI 0.31-0.91). Protection was found in all groups except the youngest, and was unaffected by adjustment for hypertension, smoking, alcohol, body mass index, and exercise. Protection from death due to stroke was greatest in recent users (RR 0.21) versus past users (RR 0.67) compared to never-users.⁵⁰

OBSERVATIONAL STUDIES OF ALZHEIMER'S DISEASE AND DEMENTIA AND HT

Paganini-Hill and Henderson⁵¹ studied death from AD and dementia in the same cohort, and found significantly reduced risk for users compared with nonusers (OR 0.65, 95% CI 0.49-0.88). The risk decreased significantly with both increasing dosages ($P = 0.01$) and increasing duration ($P = 0.01$) of oral therapy with conjugated equine estrogen (CEE). With each dose category, the risk decreased with increasing duration of therapy, with the lowest risk in the higher doses in long-term users (OR 0.48, 95% CI 0.19-1.17).⁵¹ Interpreting this study in accordance with the Theory, these patients had long-term use of HT that was initiated in the menopausal transition or at surgical menopause, and were managed for quality of life with HT to maintain eu-estrogenemia.

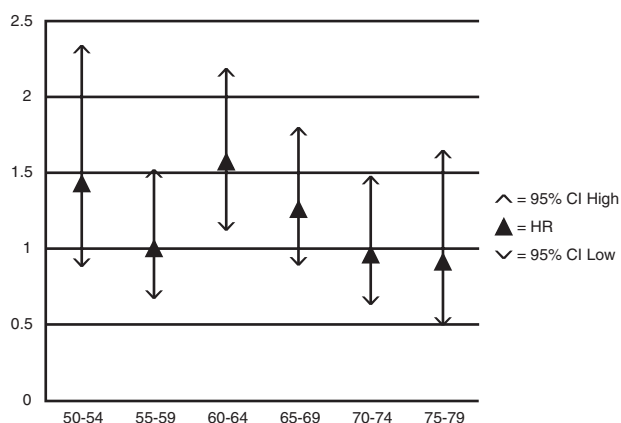


FIG. 4. Hazard ratios of renal stones with 95% confidence intervals by age groups. Reprinted from Turner and Kerber¹⁸ with permission of the publisher. Copyright © 2011, North American Menopause Society.

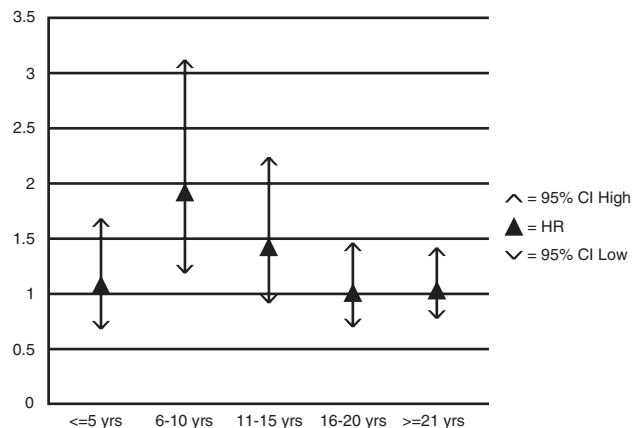


FIG. 5. Hazard ratios of renal stones with 95% confidence intervals by time since menopause at study entry. Reprinted from Turner and Kerber¹⁸ with permission of the publisher. Copyright © 2011, North American Menopause Society.

HEARING

Kilicdag et al⁵² evaluated hearing in 20 postmenopausal women on 2 mg E₂ tablets (ET), 30 menopausal women using continuous HT, 2 mg E₂, and 1 mg norethisterone acetate (NETA), and 59 menopausal controls.⁵² They identified the progestogen-related sensorineural hearing loss previously described⁵³ in the HT group, and found better low-frequency (250-2000 Hz) air conductance hearing in the ET group versus HT and control. The authors proposed ERs maintain ion and fluid balance of the inner ear, which is impaired in the postmenopausal period.⁵²

ORAL HEALTH

Paganini-Hill⁵⁴ evaluated the Leisure World Cohort for oral health. The dental survey was returned by 3,921 women in 1992. In all but the youngest age group (<70 years of age), the tooth count was higher for estrogen users in all 5-year age groups up to 90+ years. Risk of tooth loss decreased with increasing duration of ET ($P < 0.001$). Estrogen users were less likely to be edentulous than nonusers; age-adjusted RR was 0.64 (95% CI 0.51-0.79). Denture wear tended to decrease with increasing duration of use of ET ($P < 0.001$).⁵⁴ Grodstein et al⁵⁵ reported on HT and tooth loss in 42,171 women in the Nurses' Health Study in 1996. Estrogen use and number of teeth maintained were evaluated. Adjusting for age and smoking status, and having 25 teeth or more versus fewer than 25 teeth, an inverse relationship was reported between estrogen use and tooth loss, with an OR for current use of 0.62 (95% CI 0.59-0.65); for past use, it was 0.90 (95% CI 0.85-0.94). The authors postulate estrogen's anti-inflammatory properties in reducing gingivitis and estrogen's impact on mandibular bone and osteoporosis.⁵⁵

BALANCE IN EARLY AND LATE MENOPAUSAL WOMEN

Naessen et al report that disturbances of balance are treated and improved in women in both early menopause (mean age 52.5 years)⁵⁶ and late menopause (age >60 years).⁵⁷ In the

first study, 91 women were randomly assigned to E₂-norethisterone acetate regimen or placebo, and postural balance was assessed as sway velocity using a force platform. After 3 months of HT, sway velocity performance improved from baseline for the treated groups by 7% ($P = 0.007$ vs baseline, and $P = 0.038$ vs placebo) and by 12% from baseline after 6 months ($P < 0.0001$) of HT. Initiating HT soon after menopause rapidly improved balance to levels normally seen in younger women. Naessen et al's group also recruited 33 women aged 60 years or older to be randomly assigned to E₂ patches (0.05 mg/24 h) and medroxyprogesterone acetate 2.5 mg/d for 6 months or placebo. In women with low E₂ levels (<35 pmol/L, or <9.53 pg/mL), serum E₂ concentrations increased approximately 90 pmol/L (24 pg/mL) over the 3 and 6-month study periods in the treated group. HT improved the postural balance in women with low serum E₂ levels. Because improvement in sway velocity performance relative to HT in this small study (33 randomized participants) was not as dramatic in this group of older menopausal women as had been seen in the study with younger women, the authors interpreted the results consistent with the critical window hypothesis, that is, "the effects of HT on the human central nervous system are more beneficial if initiated sooner rather than later after menopause."⁵⁷ However, because late menopausal women on HT showed some improvement in performance in balance, one could postulate that the deterioration of ER function does not occur at the same rate in various organ systems remote from reproductive senescence.

EU-ESTROGENEMIA AND MEN

Eu-estrogenemia may apply to men, demonstrating Spangenberg et al's⁴⁴ assessment that estrogen is a "critical regulator of metabolism and not another ovarian hormone." An example of ER function in men is seen in ER α polymorphisms in spermatogenesis. In men with normal sperm count, those with the ER α 397T/T genotype had higher sperm concentration than those men with 397T/C and 397C/C genotypes. In men with oligospermia ($<20 \times 10^6$ spermatozoa/mL), those with ER α 397T/C and 397C/C genotypes had higher sperm motility than those with the 397T/T genotype.⁵⁸

In chronic heart failure (HF), androgen deficiency leading to decreased aromatization and thus E₂ deficiency is common in men.⁵⁹ In a Polish study of 501 men with chronic HF and reduced left ventricular ejection fraction, Jankowska et al analyzed the serum E₂ concentrations, dividing them into five quintiles. Because men with decreased serum E₂ (<12.90 pg/mL, quintile 1) or increased concentrations of serum E₂ (≥ 37.40 pg/mL, quintile 5) had different clinical pathophysiologies, the authors proposed that "deranged liver metabolism and secondary hepatocyte failure" may be the mechanism for increased serum E₂, and decreased serum E₂ may be due to the decreased amount and function of adipose aromatase, with aromatization occurring in the male adipocyte. However, the highest percentage of 3-year survival occurred in men in the middle quintile of E₂ concentration (21.20-30.11 pg/mL, quintile 3). The authors did not propose

E₂-modifying therapy, although they cited numerous experimental models of HF. We highlight this study to recognize E₂ in homeostasis. The Theory suggests that in these very sick men, there is an optimal physiological serum concentration of E₂ that yields the longest survival. The ubiquitous ERs in men in the numerous estrogen (nonreproductive) signaling pathways were functioning best in a given serum estradiol concentration (quintile 3) in very sick men. This dynamic is shown in Figure 6.

With respect to osteoporosis, men are at greater risk when bioavailable E₂ levels are below 11 pg/mL.⁶⁰ Khosla et al⁶⁰ stated that "evidence from multiple lines of investigation is now overwhelming that E₂ plays a major, and likely dominant, role in regulating bone metabolism in men."

The management of prostate cancer with androgen deprivation therapy (ADT) and risk of AD give us insight into E₂ function in men. A recent meta-analysis of 16,888 prostate cancers from electronic medical records from Stanford and Mount Sinai has shown an association of increased AD risk with ADT. There were 2,397 patients (14.2%) receiving ADT with a follow-up of 2.7 years. The propensity score-matched analysis (HR 1.88, 95% CI 1.10-3.20, $P = 0.021$) and traditional multivariable-adjusted Cox regression analysis (HR 1.66, 95% CI 1.05-2.64, $P = 0.031$) supported statistically significant negative association between ADT use and AD risk. The investigators observed increased risk of AD with increasing duration ($P = 0.016$).⁶¹ Our understanding of mitochondrial bioenergetics in accordance with the Theory leads us to conclude that removal of androgen substrate from aromatization places the prostate cancer sufferer at risk for AD.

PHARMACOGENOMICS AND EU-ESTROGENEMIA

Miller et al in the KEEPS group evaluated the pharmacogenomics of estrogens in changes in CIMT and CAC. "Twenty single-nucleotide polymorphisms (SNPs) within

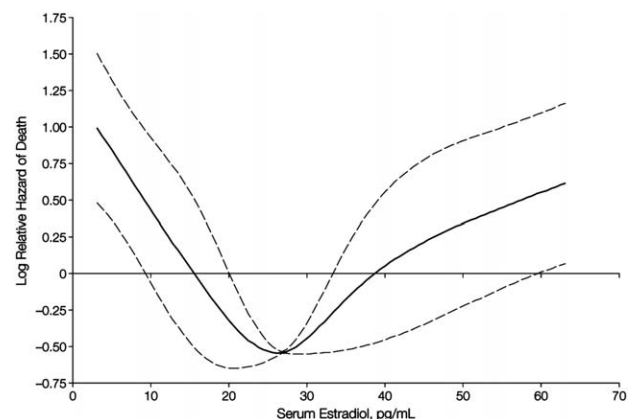


FIG. 6. Serum estradiol (E₂) by log relative hazard of death was calculated by using restricted cubic splines with five knots with 95% confidence intervals (dashed curves). To convert serum E₂ to pmol/L, multiply by 3.671. Reprinted from Jankowska et al⁵⁹ with permission of the publisher. Copyright © 2009, American Medical Association.

the innate immunity pathway most related with CIMT after 4 years were not among those associated with CIMT before HT. In 403 women who completed the study in their assigned treatment group, SNPs within the innate immunity pathway were found to alter the treatment effect on 4-year change in CIMT (eg, significant interaction between treatment and genetic variation in the innate immunity pathway; $P < 0.001$). No SNP-by-treatment effects were observed with changes of CAC above 5 Agatston units after 4 years. Results of this study suggest that hormonal status may interact with genetic variants to influence cardiovascular phenotypes, specifically, the pharmacogenomics effects within the innate immunity pathway for CIMT.” As stated by the authors in the discussion, “Additional work is needed to understand how polymorphisms in ERs contribute to development of CVD in women.”⁶² With respect to eu-estrogenemia, this is essential to understand when SNPs may indicate or contraindicate HT for a patient for menopausal therapies.

DISCUSSION

The differences in the cohorts of women in the observational studies, and the WHI and HERS RCTs have been described in numerous publications. The patients in the WHI (average age 63) had been hypo-estrogenemic for 10 to 12 years without significant VMS before starting HT in contrast to the patients in the observational studies who were more recently menopausal (hypo-estrogenemic) and “vasomotorly” symptomatic. Thus, the WHI could be interpreted as a new drug trial to evaluate the effect of CEE with or without MPA in “vasomotorly” asymptomatic chronically hypo-estrogenemic women.¹⁶ According to the theory of eu-estrogenemia, the WHI was an attempt to “re-estrogenize” women after an average hiatus of 10 to 12 years.

The numerous observational studies of the 1980s, which concluded that estrogen reduced the risk of heart disease and osteoporosis, were affected by the prevailing surgical and medical attitude of the time. Hysterectomy and bilateral salpingo-oophorectomy (BSO) was preferable to high-dose OCs to treat abnormal uterine bleeding. (Generally, physicians did not prescribe OC pills in women over age 35 years.) Hysterectomy with BSO would be recommended for an abnormal PAP smear in a woman desiring permanent contraception, and also in women with pelvic organ prolapse (during an era of Cesarean section rates of <10%) or dysmenorrhea, or with severe premenstrual syndrome (PMS), before the 1986 introduction of fluoxetine, the first selective serotonin reuptake inhibitor (SSRI).

But why oophorectomy you ask? As explained by Mattingly in TeLinde’s fifth edition of *Operative Gynecology*,⁶³ the “effect of castration on atherosclerosis or osteoporosis is not yet settled. . . physical activity has the greater role on osteoid deposition and reabsorption than any other factor. . . menopausal and post-menopausal ovaries produce androgen primarily. . . androgen is converted to estrogen (estrone) in extragonal tissue”. “(Studies) support . . . removing both ovaries after the age of between 40 and 45 who are undergoing

a hysterectomy. . . Against the disagreeable symptoms of the menopause, one must balance the possibility of malignancy developing in retained ovaries.” He wrote that the 1970’s annual US death rate was 10,000 lives from ovarian malignancy alone (1% risk in women over 40.) “Retained ovaries leave the patient at risk for pelvic pain, cystic degeneration, and asymptomatic enlargement” (thus a concern for malignancy). “Should the premature ovarian castration be performed at the age between 40 and 35, it is considered advisable that most women should receive temporary substitutional estrogen therapy, preferably with naturally occurring estrogen, to avoid estrogen withdrawal symptoms.” “. . . estrogen replacement until the average age of menopause seems a reasonable solution to the debate of the possible increased risk of coronary artery disease and osteoporosis in patients with premature castration.”

These surgical decisions were frequently made early in a woman’s estrogenemic milieu when little ER deterioration had occurred. Caring for the patient after oophorectomy was a quality-of-life decision—to feel good, take estrogen. The dose would be increased for coverage of VMS and decreased in the presence of breast tenderness. Frequently, women found 1.25 to 2.5 mg of CEEs as an optimal regimen. According to the theory of eu-estrogenemia, we believe that she was receiving genomic and nongenomic benefits from physiologic and pharmacologic levels of ET to optimize ER performance to achieve Eu-E. The Theory postulates this to be the pharmacokinetics of the Healthy User Bias.

In the previously mentioned observational studies of women on ET and small RCTs of HT use, many of whom had had hysterectomy and oophorectomy for nonhormonal conditions, we saw cohorts of women who were reported to have lower rates of various conditions such as heart disease,^{21,22} stroke,⁴⁹ eye and retinal disease,³⁷⁻³⁹ poor oral health,^{53,54} dementia,^{30,50} and osteoporosis.⁴⁸ In atherosclerosis specifically, postmenopausal estrogen replacement was an independent protective factor for CAD in a multivariate regression model ($P = 0.037$).⁶⁴

The overall morbidity and mortality of HT has dominated the debate over the past 40 years. The deaths from endometrial cancer from unopposed estrogen administration were addressed with progestin administration.⁶⁵ Modern EHR databases have shed new light on HT cessation. Mikkola et al⁶⁶ noted an increased risk of cardiac death or stroke from 1994 to 2009 in the first year after women stopped HT. The cardiac death risk was standard mortality ratio (SMR) 2.30 (95% CI 2.12-2.50). The stroke death risk was SMR 2.52 (95% CI 2.28-2.7). These rates were higher when compared with continuing HT users. This resulted in 4 more deaths/10,000 from cardiac disease, and 5 more deaths/10,000 from stroke. In the second year, the cohort of women who had stopped HT had five fewer cardiac deaths and one less stroke death per 10,000. In another study, Mikkola et al⁶⁷ evaluated users of vaginal E₂ for 10 years. There were 24 fewer CHDs and 18 fewer stroke deaths per 1,000 women. The highest reduction was in women aged 50 to 59 years. The serum levels of E₂

from vaginal HT users resulted in lower mortality rates. According to the theory of eu-estrogenemia, there were adequate serum levels of E₂ from transvaginal absorption to stabilize some ERs in nonreproductive organs.

The debate over mortality in women and HT can be seen in two other cohorts. When the WHI study group analyzed mortality data on HT cessation, they saw no change in all-cause mortality.⁶⁸ However, Sarrel et al⁶⁹ calculated that “estrogen avoidance” since the WHI, in women aged 50 to 59 years from 2003 to 2009, resulted in an estimated 18,601 to 91,610 excess deaths from women who stopped HT or never started HT.

We analyze these three cohorts (Mikkola et al⁶⁷, LaCroix et al⁶⁸, Sarrel et al⁶⁹) in the light of the theory of eu-estrogenemia, and find three distinct groups of women⁷⁰: “Women with VMS, whom we postulate were exhibiting hypoestrogenemia and suboptimal ER function, were generally excluded from the (WHI) study. The WHI cohort was a clinically healthy group of women whose various organ systems may have been functioning with metabolically compensated hypoestrogenemia.” “Physiologically, we propose that the etiology of excess mortality in the Mikkola and Sarrel cohorts was suboptimal function of some ERs due to hypoestrogenemia. Mikkola et al unmasked benefits of HT in maintaining critical regulation of metabolism and homeostasis when HT was stopped. Sarrel et al showed the consequences of estrogen avoidance on 3,600 ERs and estrogen-signaling pathways. HT that results in healthy ER function, particularly outside the reproductive system, must now be considered for women in the menopausal transition and beyond.”⁷⁰

In Thurston et al’s³² VMS CIMT study, a greater frequency of hot flashes was associated with higher CIMT and plaque. The findings in these women are consistent with the Theory (shown in Fig. 2). Thurston et al’s study provides basic science foundations to explain the stressed monkey studies by Clarkson et al⁸ and Bairey Merz et al’s^{21,22} WISE findings. In light of Thurston et al’s CIMT study, one can propose that atherosclerotic processes were beginning long before the randomization of the KEEPS⁴ and ELITE⁵ patients. These associations were not accounted for by CVD risk factors or E₂ concentration. (E₂ fluctuations were not measured in Thurston et al’s³² study.) We have proposed that the vasomotor episode is the “canary in the coalmine” that transient hypoestrogenemia is occurring,²⁰ similar to the stressed monkeys.⁷⁻¹⁰ Dr Thurston proposed additional research to elucidate other novel pathways (eg, sympathetic nervous system, hypothalamic pituitary adrenal axis). With the ubiquitous nature of ERs,^{11,12} the Theory would propose that poorly functioning ERs are partially responsible for the pathophysiology. The study by Clarkson et al would propose that restoring eu-estrogenemia early would prevent or significantly retard the progression of plaque.⁹ Mikkola et al cited that “accumulated data showing the use of E₂-based HT regimens does not endanger the heart, but rather, it significantly reduces the incidence of [CAD] events and mortality. This effect may be related to the presence of hot

flushes before HT initiation, because they may indicate a greater responsiveness of the cardiovascular system to HT. To get maximal cardioprotective efficacy of HT, a woman should initiate HT as soon as symptoms occur, and preferably within the first 10 postmenopausal years.”⁷¹ The irony of Thurston et al’s work is that the phenotype of sufferers of VMS and atherosclerotic CVD (ASCVD) that she appears to have identified is the phenotype that would have benefited most from the therapy proposed in the WHI.

We have come full circle back to Robert Wilson’s plea for adequate estrogen from puberty to grave,¹³ with the report by Levine et al⁷² that, “Menopause accelerates biological aging.” Having developed a highly accurate biological marker for age known as the epigenetic clock, the authors analyzed blood, saliva, and buccal epithelium from four studies: the WHI; Invecchiare nel Chianti; Parkinson’s disease, Environment, and Genes; and the United Kingdom Medical Research Council National Survey of Health and Development. The authors found that “increased epigenetic age acceleration in blood is significantly associated with earlier menopause ($P=0.00091$), bilateral oophorectomy ($P=0.0018$), and a longer time since menopause ($P=0.017$). Conversely, epigenetic age acceleration in buccal epithelium and saliva do not relate to age at menopause; however, a higher epigenetic age in saliva is exhibited in women who undergo bilateral oophorectomy ($P=0.0079$), whereas a lower epigenetic age in buccal epithelium was found for women who underwent HT ($P=0.00078$). Using genetic data, we find evidence of coheritability between age at menopause and epigenetic age acceleration in blood.” Using Mendelian randomization analysis, the authors found that two SNPs that “are highly associated with age at menopause exhibit a significant association with epigenetic age acceleration.” One SNP was found on chromosome 19 (SNP rs11668344; base pair position 55833664; minor/major alleles G/A; β -coefficient 0.506; $P=0.031$). In aggregate the results strongly support the causal model: menopause → epigenetic AgeAccel. The theory of eu-estrogenemia would argue for HT to forestall the epigenetic age acceleration effects (AgeAccel) and a deterioration of ERs.

CONCLUSIONS

In consideration of all of the above, we propose evidence is mounting to understand the healthy user bias of “pre-WHI” HT observational studies. ET was started shortly after oophorectomy in premenopausal women before significant deterioration of ER function, and was probably given in doses that maintained ERs with pharmacologic (nongenomic) and physiologic (genomic) estrogen concentrations which were higher than “lowest dose for shortest duration.” HT—either ET or ET plus cyclic progestogens—was started with vasomotor instability or menstrual irregularity 2 to 7 years before the last menses. The empiric treatment goal was to optimize patient-directed quality of life.

Quality of life is the reason that women frequently give when they desire to extend HT use beyond set ages, for example, age 60 or age 65. The 2015 NAMS Position Statement affirms the use of systemic HT on an individualized basis.⁷³ The Theory considers the historic HT use by the healthy user cohort, ER function in the various organ systems that we have discussed, and Mikkola et al's epidemiological data.^{66,67}

In conclusion, estrogen is a "critical regulator of metabolism."⁴⁴ Estrogen action through ERs is critical for homeostasis in women and men (aromatization). The paradigm shift becomes the focus of ET to maintain healthy ERs. Considering there are more than 3,600 ubiquitously distributed ERs and signaling pathways,¹² it is biologically naïve to conclude that estrogen, with its complex genomic and non-genomic actions, should be deficient from a menopausal woman's body.

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