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Guest Editorial

The clinical practice impact of the Women's Health Initiative: political vs biologic correctness

1. Introduction

In the wake of the publication of the Women's Health Initiative (WHI) results [1], numerous comments and position statements were issued, most of which endorsed the conclusions of the WHI researchers: in essence, this would limit the prescribing of hormone therapy to symptomatic menopausal women, for a period of 4–5 years. There was however, one editorial comment [2] that posited *the* question and which goes to the core issue of whether there is a sound biologic rationale for the prescribing of HT. They stated 'Survival of the human species over two million years implies that female sex hormones by themselves are not dangerous to health. If harm is established, we must therefore examine the types of substitutes that we use and their means of delivery.' A fundamental question that this raises and which needs to be addressed and answered is: what differentiates the women who experienced adverse events after taking HT from those who did not; and the reverse of that question: what factors protected those women who on HT did not have an adverse event. The numbers speak for themselves and help place the entire issue into an appropriate clinical perspective. The effect of combination hormone therapy (CHT) on the risk of coronary artery disease (the primary goal of the WHI) revealed that 37 vs 30 events in treated vs control women suffered a CHT event annually per 10 000 women. A similar minority of women were adversely affected when the risk of CHT related breast cancer was examined: 35 vs 30 events annually of 10 000 women on CHT and placebo, respectively. This difference in subject behavior is illustrative of fundamental flaws in at least 3 basic WHI assumptions: all 'healthy' postmenopausal women have the same biologic characteristics; the pathogenesis of cardiovascular disease is causally related to the onset of the menopause and that all estrogens and progestogens are bioequivalent.

2. The menopause is a unique and individual event

There are only two facts referable to the menopause that are applicable to all women: the menopause is a natural life event that every woman will experience; the common denominator is cessation of menstruation. For the rest—symptoms, risk of CHD, osteoporosis, breast and colon cancer, Alzheimer's disease—every woman is as unique as her own thumbprint. The notion that all menopausal women need HT or can be treated with the same dose and type of HT, is and always has been irrational and inappropriate.

Much progress has been made in the last decade to explain the clinical diversity and needs of menopausal women. Central to this issue is the identification of at least two estrogen receptors (alpha and beta) and the complex interaction of various ligands that, modulated by co-initiators and co-repressors (including ER beta), influence the activity of a given tissue, in a given organ, in a given woman [3]. It is the heterogeneity in alpha and beta estrogen receptors, plus the genetic control of enzyme systems that regulate estrogen synthesis, metabolism and catabolism, that might for example, determine the predilection of certain women for breast cancer [4]. In this respect, the notion that all menopausal women are estrogen

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deplete, is false. All menopausal women are deficient (relative to premenopausal women) to a variable degree. The need for estrogen therapy will vary with the amount of endogenous estrogen being synthesized, the 'estrogen threshold' for a relevant organ (brain, bone, and heart) and based on this requirement, the amount of estrogen that should be prescribed. Thus all postmenopausal HT is 'additive' and in this sense is best regarded as 'pharmacologic' rather than 'physiologic' therapy. As with any other drug, the least amount required to produce a desired clinical response is the 'best' dose to prescribe.

Advances in technology do allow the identification of women, who although asymptomatic, will be at risk or have latent evidence of conditions such as osteoporosis, CHD and breast cancer. Two examples illustrate this point: postmenopausal women with normal levels of endogenous estradiol (< 20 pg/ml) and whose values are in the upper quartile will be at greater risk for breast cancer than women with mean E2 levels below 5 pg/ml [5]; conversely, women with upper quartile but 'normal' menopausal E2 levels will be at lower risk for osteoporosis [6]. Women who metabolize their estrogen via the D vs A ring pathways are at increased risk of breast cancer, as are women who have higher levels of sulphatase aromatase and 17beta hydroxysteroid dehydrogenase activity in their breast tissue [4]. These are just a few examples of the variables that may explain why some women are vulnerable to hormone associated breast cancer, while the majority are not.

Clinical indications of women at risk include: dense breast on mammography (pretreatment); high bone mineral density and a family history of breast cancer; baseline high sensitivity E2 levels in the upper quartile of normal (or above) will further identify 'higher risk for breast cancer' women vis à vis their estrogen status and therefore their suitability for HT. Further analysis of the WHI data may be helpful in answering this issue.

CHD is a complex multifactorial disease. The biologic rationale for the protective role of ET has been clearly established and validated in numerous basic science and observational studies [7]. Why then, did a few women on HT develop adverse CHD events while the vast majority of women, given the same treatment, did not? Only two possibilities will be briefly reviewed. Patients had their HT discontinued if they had triglyceride levels in excess of 1000 mg/dl. This presumes that patients with raised triglyceride levels (400–1000 mg) were not excluded from (a) entering the study or (b) continuing on HT. Hypertriglyceridemia is an excellent surrogate biomarker for both insulin-resistance and hypercoagulation, and may be negatively impacted by the type and dose of combination HT [8]. More importantly, women with hypertriglyceridemia define a sub-group of women who, although classified as 'healthy normal' at baseline, are in fact at significant risk of asymptomatic CHD. This was found to be the case in a subanalysis of inflammatory biomarkers and incident Coronary Heart Disease from the WHI observational study [9]. Among 75 343 women with no history of cardiovascular disease or cancer, 304 women developed incident CHD when compared with 304 matched women who were event free for the 3 years of observation. The result: C-reactive protein (CRP) and the cytokine interleukin 6 independently predicted vascular events among apparently *healthy* postmenopausal women, and that this was related to the *base-line* levels of the inflammatory biomarkers, and *not* HT-related increase in CRP.

2.1. The clinical message

Simply put, there is solid biologic data to explain why all menopausal women are not the same. This may explain why some women (a minority) may be at risk of complications when exposed while others (the vast majority) do not suffer any ill effects and may indeed benefit from supplemental HT. The clinical challenge is to develop cost-effective strategies that will accurately define healthy women from women with asymptomatic latent disease. The former group will benefit from selective HT; the latter require medications specific to their underlying disorder.

3. Defining primary and secondary prevention: windows of therapeutic opportunity:

3.1. Cardiovascular heart disease

Of the 8506 women in the estrogen and progestin arm of the WHI study, 33.4% were aged 50–59: 45.3% were between 60 and 69 years of age and 21.3% were aged 70–79 years. The pathogenesis of atherosclerosis has been well defined, and it has been clearly established that early fatty streaks are detected in aortic and coronary artery tissues from a very early age (childhood and adolescence) and that there is evidence—to a greater or lesser extent—of coronary artery atheroma in most, if not all, western women by the age of 50–55 years. To suggest therefore, that the WHI was based on 'healthy' women and was designed as a 'primary prevention' study is to deny the reality of the natural progression of CHD and of the degree and prevalence of CHD in this cohort of 'healthy' women. Further, the term 'primary prevention' should be re-defined. As indicated in Fig. 1, there is indeed a 'window of therapeutic opportunity' to prevent CHD: this occurs well before the menopause and is reliant on exercise, good nutrition and an appropriate lifestyle. Central to the success of this primary prevention program in women, is intact ovarian function. Women with primary ovarian failure (Turner's syndrome) and non hormone-substituted premature menopausal women (surgical or idiopathic) are at increased risk of CHD. Hormone replacement—in the *true* sense of the phrase—reduces this risk.

Estrogen has been shown to prevent or modulate the progression of atherosclerosis both via its effect of hepatic factors (involving lipid–lipoprotein: carbohydrate metabolism; hemostasis and inflammatory proteins and cytokines) and directly on the coronary artery smooth muscle: limiting smooth muscle cell hypertrophy; influencing coronary artery vasoreactivity [7]. The timing and type of HT intervention is critical; early perimenopausal and immediate postmenopausal therapy will ameliorate the degree of atherosclerosis and help to stabilize the plaques' fibrin capsule. In this context ET may serve as an effective 'secondary intervention'. Later treatment of women with certain types of atheromatous disease (fatty plaques) may have an adverse response: rupture of the fibrin capsule with an increased risk of thrombosis. In addition, negation of estrogen's vasodilatory function by certain progestogens may compound the situation for many women. This is especially true for medroxyprogesterone acetate (MPA) [10]. Future data analysis may help to clarify this issue. Given the current climate however, it is unfortunately highly unlikely that the CHD protective

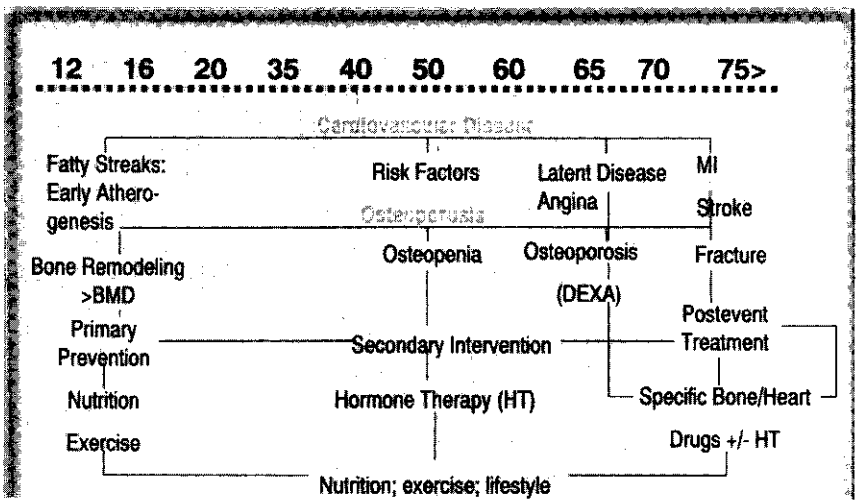

Fig. 1. Timeline: redefining disease prevention and health promotion intervention.

potential of ET/HT will ever be put to the test. However, absent this data, the potential 'adverse' CHD effect of ET/HT should not, in the author's opinion, preclude the selective long-term use in normal women with proven low CHD risk—from being used as a preventive or a treatment for osteoporosis.

3.2. *Osteoporosis*

The bone remodeling cycle is influenced by both estrogen and androgens. The latter, by direct binding to testosterone and dihydrotestosterone receptors and by aromatization to estradiol with ligand binding to the estrogen receptor. Estrogen (E2) initiates the transcriptive activity of the bone cells via genomic and non-genomic pathways. Estrogen and androgen receptors are present on the bone resorptive cells (osteoclasts), the bone forming cells (osteoblasts) and the modulator of the balance between these two cells, the osteocytes [11]. The activity of these cell-types is up-regulated in the presence of estrogen, and decreased with estrogen/androgen deficiency. The net result is the accrual of bone during adolescence, maintenance of bone mass till just before the menopause, and a 4–5% annual loss of bone mass in the first few years postmenopause. Estrogen substitution prevents postmenopausal bone loss and results in a measurable and progressive increase in BMD—as long as HT is used. Estrogen is essential for the osteogenic influence of exercise, increases intestinal and renal calcium absorption and has an inhibitory influence on parathyroid hormone activity. In some studies estrogen has been shown to improve balance and stability, and prevent falls. Estrogen use is responsible for the up-regulation of osteoblast progesterone receptors [12]. This may explain why combining estrogen with an androgenic progestogen increases BMD to a greater degree than E2 alone therapy. Recent studies have indicated that lower doses of ET—both oral and transdermal—are able to maintain BMD, but can also increase BMD in a dose related manner [13].

Further, additional research suggests that the strength of bone following ET may be related to the type and orientation of bone collagen, and the prevention of vertebral bone trabecular plate perforation, and resulting micro-architectural damage. Thus the numerous observational studies that have documented reduction in vertebral and hip fractures following HT have an obvious and sound supportive biologic rationale.

All of estrogen's bone protective functions are physiologic and many are not common to other anti-resorptive agents [14]. The long-term effect of biphosphonate on bone (in excess of 10 years) is not known, nor can the long-term safety of SERMS such as Raloxifene, be compared with 60 years of clinical experience with ET. Substitution of these products for the primary prevention of osteoporosis in recently menopausal is predicated, not by the ineffectiveness of ET, but out of concern for its long-term consequences on CHD and breast cancer. However, examination of the WHI data [1] shows that except for year 5 of follow up following randomization, the ratio of CHD clinical events, comparing patients in the hormone vs the placebo group, decreased over time i.e. there were fewer HT related CHD incidents. The ratio's HT/placebo CHD events from year 1 to 6 were: 1.78; 1.15; 1.06; 0.99; 2.38; 0.78.

3.3. *Not all hormones are created equal*

The authors of WHI concede that the result of the study was based on one preparation: conjugated equine estrogen 0.625 mg and MPA 2.5 g. The non-pregnant human female synthesizes two estrogens, both of which are derived originally from androgens, estradiol and estrone. The pharmacokinetics and pharmacodynamics of exogenous estrogen therapy is well established and validated. Depending upon one's intent, it is possible to replicate a premenopausal estrogen milieu with a greater E2:E1 ratio; or the E1:E2 response predominance characteristic of postmenopause. The former objective will require transdermal or percutaneous E2 administration; the latter, the oral use of E2. The choice of E2 route should be determined by patient preference and medical need. For example, women with low levels of HDL-cholesterol will benefit more from *oral* ET; women at high risk of breast cancer (especially in the presence of excessive breast sulphatase

activity) would be at lesser risk if *transdermal* ET is prescribed. Dosage is a further key issue, as is the biologic availability of the prescribed ET. Both are interrelated. Because of the hepatic stimulation of SHBG by oral estrogen, approximately 2 mg of oral 17beta estradiol results in the same amount of free E2 as that from a 50 mcg E2 patch. The amount of SHBG produced varies with the type of estrogen too: 0.625 mg of CEE increases SHBG by 100% from baseline after 3 months of therapy, compared to 42% following 1 mg of oral 17beta estradiol [15]. Newer studies have indicated that comparable results of lower-dose ET regimens have been obtained when compared with previous higher 'traditional' doses [16]. The clinical message: choose the lowest dose of estrogen to achieve a given therapeutic goal and titrate and adjust the dose according to the patient's response. Unfortunately, the logic of this approach is unlikely to be tested in a study that parallels that of the WHI—both because of the cost and the complexity of designing a study that truly replicates the reality of clinical practice.

The estrogen-therapy alone treatment arm of the WHI is still continuing, thus it is possible that the adverse results of the WHI report are due to the progestogen. This subject is *deserving of its own editorial*, since the various issues are complex, incompletely understood and deserving of detailed analysis [17]. The following few brief comments summarize some of the more pertinent issues:

(1) Unlike estrogen and androgen, progesterone is not synthesized in significant amounts and is not 'natural' to postmenopausal women.

(2) In premenopausal women, progesterone is present in the later phase of the menstrual cycle. Progesterone has an inhibitory effect on endometrial cells, but induces proliferative changes in breast tissue. Because of its cyclic production and withdrawal, menstruation usually occurs on a monthly cyclic basis.

(3) Progesterone is indicated in post-menopausal women for only one reason: inhibition of the endometrium and the prevention of estrogen-induced endometrial hyperplasis and cancer.

(4) To encourage compliance with combination HT, the concept of continuous combined ET and progesterone therapy was introduced, with the objective of a 'bleed free' regimen—one that is especially acceptable to older postmenopausal women.

(5) To achieve this goal, progestogens rather than progesterone were added to estrogen therapy. Those derived from progesterone e.g. MPA have a different metabolic profile, compared with progestogens of androgenic origin e.g. norethindrone acetate (NETA). Examples of differences on cardiovascular health and function are: MPA more so than NETA may antagonize the anti-atherogenic effects of estrogens [18]; significantly enhance proliferation of coronary artery smooth muscle cells [19]; up-regulates thrombin receptor expression (and hence the increased risk of thrombosis) due to its glucocorticoid activity [20], can potentiate endothelin I induced coronary artery vasoconstriction; and does not attenuate the estrogen-induced increase in triglycerides [16].

(6) Micronized progesterone and some other synthetic progestogens e.g. dydrogesterone [21], have less of the potential side-effects noted for MPA. However, there are few head-to-head comparisons to fully justify this conclusion.

3.3.1. Clinical message

In an attempt to encourage compliance with combination HT, the introduction of the 'bleed free' CHT approach *may* have compromised the long-term safety of these preparations for a few menopausal women. This is *not true for most menopausal women.* Further, lower doses of progestogen in combination with comparably lower amounts of estrogen, may result in fewer adverse events and maintain an acceptable bleeding pattern. The use of cyclic progesterone or the use of intra-uterine medicated IUD's *may* further enhance the safety of combination HT.

4. Conclusion: political vs biological correctness of the WHI report

The WHI report concluded with the following statement: 'results from WHI indicate that the combined postmenopausal hormones CEE 0.625 mg/d, MPA 2.5 mg/d, should not be initiated or continued for the primary prevention of CHD. In

addition, the substantial risks for cardiovascular disease and breast cancer must be weighed against the benefit for fracture in selecting from the available agents to prevent osteoporosis' [1]. This statement has been endorsed by many of the influential medical associations in the USA, despite the fact that the WHI was *not* a primary CHD prevention trial and that their definition of 'healthy postmenopausal women' has ignored the heterogeneity of the menopausal transition. Although the authors of the WHI are careful to note that the HT used in the trial involved only one product, the implication of their argument includes all other HT—until proven otherwise. Therein lies the problem: the practice of medicine is dominated by the burden of providing 'evidence'—not on biologic grounds as in the past—but on the new 'gold standard' of large population-based randomized clinical end-point trials. Biologic based medical care—to which the author subscribes—has been dismissed by the RCT proponents as being 'mechanistic' and providing a false premise on which to base medical care. Validated basic science, applied human research and astute clinical observation are complimentary to each other and indeed, form the basis for 3 of the sciences on which medical training and practice is founded; physiology, pathology and pharmacology. All randomized clinical drug trials—short- or long-term, small or large—base their eventual conclusions on the outcome of the *group's* response to a given therapy. Within that cohort, there are those that will respond and those that will not. Examination of scatter gram plotting of the data illustrates this point more effectively than the usual 'mean ± SEM' numbers, method of reporting. In this context, it is more meaningful and realistic to inform a patient that *her* annual increased risk of a HT-induced cardiovascular event is 7:10 000 (assuming that she has the same health profile as the women in the WHI who experienced these events) than it is to base one's advice on a consideration of the O'Brien-Fleming boundaries, adjusted by the Bonferroni correction of the Global Health Index. Yet, highly qualified and experienced scientists and physicians from well respected organizations have chosen to base their advice on the newly accepted standard of RCT with clinical end-point outcomes. Is this the correct approach? Time will tell. In the interim, how should physicians respond to their patients' questions and needs?

1) Educate yourself and inform your patient viz a viz the scientific rationale for the use of HT.
2) The patient must have a valid indication for HT.
3) The type and dose of HT must be individualized for a given indication at a given point in time.
4) The lowest effective dose of HT should be prescribed, re-evaluated annually and adjusted to the woman's clinical response and needs.
5) There is no single preparation that is suitable to all women.

In short, the argument is not an issue of what is 'politically correct' or 'biologically correct', but what is right for the individual patient. Whereas organizations have societal obligations, the physician in clinical practice has only one responsibility: ensuring the health and well-being of his/her patients, one at a time. Thus, the decision whether or not to take HT rests between the physician and the patient.

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