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A decade post WHI, menopausal hormone therapy comes full circle – need for independent commission

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ABSTRACT

The sudden decision by the National Heart, Lung, and Blood Institute of the National Institutes of Health to terminate the estrogen–progestogen therapy arm of the Women's Health Initiative (WHI) Study a decade ago now begs two questions: – has women's health after menopause been helped or harmed as a result of the findings and the way in which they were presented, and, if harmed, what needs to be done to put things right? Time and multiple reviews of specific publications from the WHI lead to the serious question whether a project designed to be of benefit to women's health has boomeranged, and instead may have resulted in significant impairment to both the quality of life and physical health of postmenopausal women. It is therefore urgent to confirm whether this is so and whether corrective action needs be taken to prevent even more harm.

There are two obvious and immediate actions to be called for:

(1) The Food and Drug Administration (FDA) needs to revisit the black-box warnings on postmenopausal hormones. Specifically, there needs to be a separation of the advisories for estrogen alone from estrogen and progestogen combined usage.

(2) Justification is given to call for an independent commission to scrutinize every major WHI paper to determine whether the data justified the conclusions drawn.

Women progressing through and beyond menopause in the next decade need to be spared the unnecessary harm that may have been inflicted on their sisters of the previous decade.

BACKGROUND

The sudden decision by the National Heart, Lung, and Blood Institute (NHLBI) of the National Institutes of Health (NIH) to terminate the estrogen–progestogen therapy arm (EPT) of the Women's Health Initiative (WHI) Study a decade ago now begs two questions: has women's health after menopause been helped or harmed as a result of the findings and the way in which they were presented, and, if harmed, what needs to be done to put things right?

At the time of the initiation of the WHI, world-wide utilization of postmenopausal estrogen and progestogen therapy, except for isolated areas within the United States, was mostly limited to therapy of menopause-related symptoms in women aged between 40 and 60 years, largely vasomotor symptoms and those related to vulvovaginal atrophy, and for prevention of osteoporosis. Even then, over 75% of women starting postmenopausal hormone therapy (PHT) stopped filling their prescriptions within 24 months. Within the United States, there was a growing tendency to prescribe combinations of these hormones for prevention of cardiovascular disease.

Because of the latter tendency, the WHI study was initiated with the primary objective of determining whether the observational studies demonstrating a cardioprotective effect of

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OPINION

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PHT were correct. The truth is that the WHI was a study designed by the NHLBI of the NIH, largely by cardiologists and epidemiologists, initially without accurate input from reproductive endocrinologists or menopause experts. The WHI study was never designed to investigate menopause *per se*, or the efficacy of hormones for therapy of menopause-related symptoms. Indeed, symptomatic women were largely excluded from the study to reduce the likelihood of dropouts in a long-term study. Moreover, to ensure adequate numbers of cardiovascular events to power the study, the age range was set as 50–79 years, with a majority of the volunteers being a decade or more beyond their menopause. Obviously, the older the population studied (in turn, the further they were away from menopause), the higher the incidence of heart attacks, strokes, and thromboembolic events, and therefore the fewer the number of study patients necessary to be enrolled.

A firestorm in women's health ensued when the EPT arm of the WHI was prematurely terminated because of *'increases in breast cancer, coronary heart disease, stroke, and pulmonary embolism in study participants on estrogen plus progestin compared to women taking placebo pills. There were noteworthy benefits of estrogen plus progestin, including fewer cases of hip fractures and colon cancer, but on balance the harm was greater than the benefit'*[1]. The news, announced at a hastily convened press conference on July 9, 2002, at which the outcomes were over-stated to the media as percentages of relative risk, was immediately followed by an early publication in *JAMA* entitled: 'Risks and benefits of estrogen plus progestin in healthy postmenopausal women'[2].

Spokespeople for the WHI at the press conference cautioned against all use of estrogen and progestin hormone therapy after menopause, citing public health concerns.

The nature of the exaggerated, misleading, and sensationalistic first announcement was recognized by an informed few, but missed completely by the media and much of organized medicine. One of my earliest medical editorials to comment on the issue concisely expressed the concern: '*While the merits and demerits of the data and the wisdom of the decision to terminate this arm of the WHI study will be debated for years, the manner in which the study was terminated was poorly planned, abrupt, and inhumane. Predictably, the media response was enormous, ranging from thoughtful to sensational. Panic was caused, numerous women discontinued therapy, and women and their health providers alike have been thrown into a state of confusion, distrust, and quandary of what to do next*'[3].

The initial 2002 WHI conclusion that harm was greater than benefit appears to be the result of two factors. The negative perception of the outcome data was clearly magnified by its concentration on percentiles of relative risk, rather than the pertinent issue to women of absolute risk, and exaggerated by the use of a new concept called the 'global health index' (GHI). The second factor was the lumping of all the outcome data into one group and not by decade of age, as defined in the study's own protocols, or time since menopause[2,4,5].

The title of their very first report in *JAMA* in July 2002 defines their misinterpretation of the results from the outset: 'Risks and benefits of estrogen and progestin in healthy postmenopausal women'[2]. Their population was neither completely healthy, nor simply postmenopausal. Women up to 79 years of age were started on hormones. Even at that time, it would have been extremely unusual clinical practice to start hormones in women over 70 years, and certainly in doses that would not have been considered appropriate for their age. Had the title been something like 'Risks and benefits of initiation of estrogen and progestin in women aged 50–79 by decade of age and time since menopause', and the authors strictly interpreted and discussed their results and conclusions in that way, the WHI investigators would not be playing on the defensive as they are at this time.

These issues raised serious questions about the credibility of the WHI Writing Groups and hence of the NIH as well[2–4].

THE INAPPROPRIATE USE OF A NON-VALIDATED INDEX

As the WHI study progressed, the investigators had pondered on how to balance risk and benefit and created a non-validated instrument which they termed the GHI, an outcome tool that was not part of the original study design. They then relied on the results drawn from this non-validated GHI information to reach absolute conclusions and these were generalized to all women aged 50–79. This non-validated index, based on the first occurrence of one of several predefined events, was then used by WHI investigators as the defining mechanism to balance the risks and benefits of PHT, and to develop conclusions and recommendations for public health policy and clinical practice[2,5].

As early as 2004, I challenged the credibility of the WHI interpretation of equivalence of impact of outcome of different diseases[5]. The entire science of ranking clinical outcomes with proven and validated tools such as cost-effectiveness analysis using quality-adjusted life years (QALY), measuring a trade-off between longevity and quality of life, had been completely ignored by the WHI investigators. Instead, they chose to base their complete interpretation of the outcome of their data on the non-validated GHI. My early critique of the GHI commented that any '*clinician who has spent time with patients suffering with various chronic diseases could recognize that one disease is not equivalent to another. In this day and age, for example, it is far easier – medically and emotionally – on the majority of women to be treated for early-stage breast cancer than to be immobilized by severe backache following osteoporotic vertebral crush fractures… Each disease has outcomes that can be measured by subjective and objective values. Therefore, it is totally unacceptable in this day and age to report the outcome of any specific therapy with multiple potential positive and negative endpoints, such as heart attack, thrombosis, dementia, and fracture, as if each of these were an equivalent event*'[5].

Recently, the WHI Writing Groups have become inexplicably reserved in utilizing the GHI. Have they accepted that one case of breast cancer is not equal to one heart attack, or one

stroke, or one fracture? Or have their latest results actually shown that, in specific populations, notably younger women, the GHI really demonstrates a potentially favorable outcome?

In terms of expressing outcomes as relative risk instead of absolute risk, it cannot be emphasized enough that, with the exception of stroke in older women and venous thromboembolism in the first 1–2 years of therapy, the absolute levels of risk and benefit in all outcomes reported by the WHI studies all fall into the World Health Organization categories of rare or very rare.

SO WHAT WAS THE WHI ALL ABOUT AND WHERE DID THE WHI WRITING GROUPS GO WRONG?

To repeat, the primary objective was to determine the balance of risk and benefit when older women were given estrogen therapy (ET) or EPT for potential prevention of coronary heart disease. This was never a study about menopause.

Many of the reports from the WHI demonstrated some degree of disconnect between the specific study objectives, parameters, and results, from the discussion and conclusion sections of their reports, without exception taking a 'glass half-empty' approach, and embellishing the negative findings at the expense of the positive. It seems that defending their misinterpretation of the 2002 data became more important than accepting the scientific facts out of their own data. The protective guise of 'interest in public health' is often out of synchrony with the data being presented[6,7]. The observational studies largely confirmed the findings of the other major observational studies. The sub-studies and sub-analyses in relation to menopause can be dismissed as largely 'noise' because of the skewed selection of their study participants. Even the much-publicized Women's Health Initiative Memory Study (WHIMS) can be ignored as irrelevant to menopause because women were started on higher doses of conjugated equine estrogens and medroxyprogesterone 15 or more years beyond menopause[8].

If we look at their most recent data on absolute risk in the populations studied, broken down into age groups, and as far as possible into time of onset of drug therapy since age of menopause, what do the numbers look like?

The data for the estrogen-only groups and the absolute risks are revealing. In the women less than 60 years of age, estrogen compared to placebo showed a reduction in major adverse effects per 10 000 treated women annually of 11 fewer cases of coronary heart disease, 2 fewer strokes, 14 fewer cases of diabetes, 8 fewer breast cancers, 56 fewer fractures, and 10 fewer deaths. The only adverse event to demonstrate an increase by estrogen over placebo was deep vein thrombosis/pulmonary embolus with 4 extra cases, occurring largely in the earlier years of use[9–12]. Perhaps even more striking are the 2007 data that show a clear statistically significant reduction of risk of coronary heart disease for women on EPT in the WHI who were less than 10 years from menopause as compared to women who were more than 20 years from menopause[9]. Surely these data were available to the limited group of individuals who took upon themselves the task of writing the first report in 2002?

These results make eminently clear why the GHI is less emphasized. The WHI investigators conclude that these results actually do converge with information from observational studies, animal studies, and laboratory studies, and that their results support that the health consequences of hormone therapy may vary by duration from menopause[9]. However, they do not conclude that benefit might outweigh risk in this younger group. Why?

WERE WOMEN HARMED BY THE PUBLISHED WHI STUDY CONCLUSIONS AND RECOMMENDATIONS?

Literally millions of women discontinued hormone use after the dramatic announcement by the NIH in 2002. The real story of the WHI may turn out to be incalculable damage wrought on younger peri- and early postmenopausal women who discontinued their therapy and who are now several years beyond menopause and off hormones. Not only have they have suffered through menopause-related symptoms, but the very women who might have been protected from heart disease, the single biggest killer of women over 50, and osteoporosis, one of the most significant causes of long-term disability, are the ones potentially most damaged by the WHI[13]. Women who discontinued PHT have significantly increased risk of hip fracture compared with women who continued taking PHT[13]. Indeed, there are estimates that discontinuation of PHT may have resulted in over 43 000 bone fractures per year in the USA. The number of increased cardiovascular events in young women who discontinued ET may be even more staggering. Publications from the WHI clearly demonstrate no increase in cardiovascular risk in women aged 50–59 years and, indeed, for the first time ever, an intervention, namely estrogen, has been demonstrated to actually reduce calcified plaque burden in the coronary arteries of these women[9–11]. Even statins have not been demonstrated to be this effective in women.

This is a remarkable outcome. Given that almost 50% of women will die from cardiovascular disease, the public health impact of this response could be enormous.

Instead, the women who discontinued PHT a decade ago probably should not contemplate starting again because they are in the older age group, further away from last exposure to estrogen, and more likely at higher risk for thrombosis, heart attack and stroke. 'The last nail in the coffin of hormone therapy', the mantra often repeated by WHI supporters, might actually have caused the exact opposite outcome of what they had originally hoped and anticipated, an infliction of increased morbidity and mortality and impaired quality of life on early postmenopausal women. This is a burning question in need of an immediate answer.

ARE WE BACK WHERE WE STARTED A DECADE AGO?

Since mid-2002, there has been a plethora of comment locally and internationally in the general and scientific press with opinions running for and against the WHI statements. Moreover, the WHI has continued to present new data, and a surfeit of analysis, sub-analysis, and re-analysis. Almost certainly, this acrimonious debate could have been avoided.

The most contemporary comprehensive literature analysis and recommendations for use of PHT is to be found in the latest position statement on postmenopausal hormone therapy from The North American Menopause Society (NAMS)[14]. Essential reading for anyone in clinical practice, and indeed all providers and payers of health care, as well as government agencies, most specifically the FDA, the conclusion of the paper speaks volumes: *'Recent data support the initiation of HT around the time of menopause to treat menopause-related symptoms and to prevent osteoporosis in women at high risk of fracture. The more favorable benefit–risk ratio for ET allows more flexibility in extending duration of use compared to EPT where the earlier appearance of increased breast cancer risk precludes a recommendation for use beyond 3 to 5 years'*[14]. After the entire hullabaloo created by the WHI, the current recommendations for postmenopausal use of hormone therapy are virtually back to where we started.

Ten years ago, millions of women were on various forms of estrogen and progestogen, mostly for control of menopause-related symptoms, but also for protection against bone loss, and for some, to reduce the impact of cardiovascular disease. A decade later, NAMS in its 2012 HT position paper is making the same recommendations and also suggesting women with early or premature menopause take hormone therapy at least until the median age of normal menopause. Yet the number of prescriptions has dropped by nearly 75% compared to 2002. Have the women who have rejected the concept of hormone therapy because of fear of cancer and other problems so exaggerated by the WHI reports suffered unnecessarily? Time and population studies may give us an answer, but most certainly women with severe symptoms should be reassured by the current state of knowledge.

Certain questions need to be raised about the behavior of the WHI investigators and Writing Groups. Why did the WHI investigators not present the July 2002 data in 10-year subsets? They clearly already had those results, as demonstrated by the demographic details presented in that paper[2,9]. Was it perhaps because the subsets demonstrated different outcomes, and the only way the 2002 WHI results could claim a difference on their 'GHI' was to present the merged data? In an article criticizing the WHI, the lead author was quoted in the *Wall Street Journal* (*WSJ*) as saying '*Our main job at the time was to turn around the prevailing notion that hormones would be useful for long-term prevention of heart disease. That was our objective. This was a worthy objective which we achieved*'[15].

The WHI responded to that *WSJ* article with a complete *non-sequitur*, stating *'The younger women who took estrogen-alone had less coronary calcium than the women who didn't take the drug, suggesting that estrogen-alone might offer some benefit for heart disease in the short term. But since there was no reduction in clinical heart disease in older women, it would be unwise to presume that any benefit in younger women would persist into older ages if women continued to use estrogen'*[16].

The WHI response was both defensive and absurd. Observational data from large studies like the Nurses' Health Study have shown a protective effect when women starting at a younger age are followed over time, and such evidence was the catalyst to the initiation of the WHI study itself. The whole premise of contemporary research is that the early initiation of estrogen directly retards atherogenesis. Clearly, the younger women starting hormones in close proximity to menopause need to be followed up for what occurs later, and, as the WHI was prematurely terminated, there is unlikely to be any answer to this vexing question forthcoming from the WHI. They simply failed initially to recognize the variance of effect on the younger women and did not follow up for long enough. They cannot compare this younger group to the older women who had a considerable period of non-exposure to estrogen before initiating therapy at an older age.

So, while the WHI data in relation to the early menopausal woman are in complete alignment with the observational studies, clearly demonstrating that benefits outweigh risks, most definitely in women treated on estrogen only, the women themselves remain in fear of PHT and continue to be influenced by the early misrepresentations of the data by the WHI[12]. Enormous damage has already been inflicted on the last generation of early postmenopausal women. But what can be done for the current generation now traversing the perimenopause?

IT IS TIME TO DETERMINE THE TRUE FACTS

In my personal opinion, the conclusion to be drawn from this entire episode is that a project designed to be of benefit to women's health has boomeranged and instead may have resulted in significant impairment to both quality of life and physical health of postmenopausal women. This is clearly a harsh indictment and it therefore becomes urgent for an appropriate independent evaluation of the key publications out of the WHI to be taken to confirm whether there was irresponsibility that needs to be identified and admitted. In that case, urgent public relation and education steps would need to be initiated before even more harm could be inflicted on women's health.

At the expense of repetition, had the WHI kept to its original study objectives and reported the results impartially and by decade of chronological age and time from menopause, the study would not have been subject to the international

disapproval that it received. This is unfortunate because there are some pertinent data coming out of some the studies of the WHI. Regrettably, it is now past the time that the NIH can bring all their WHI investigators together to develop a transparent and comprehensive summary of their results – they have quite simply lost the public trust, as have many of the investigators who placed their names on papers with questionable conclusions, unjustified by their own data hidden in the results of those papers. An egregious example of this disconnect between results in the data section of the paper and the conclusions drawn in the discussion and summary section is the publication on ovarian and uterine cancer[6]. When I challenged the paper for an unjustified exaggeration of risk[17], in this instance the WHI Writing Group acceded to their error[7]. Now every major WHI paper needs to be scrutinized under the same microscope to determine whether the data justified the conclusions drawn, and those doing the review cannot be members of the WHI Writing Groups alone. My prime objective at this time is to request an independent review of all the key WHI papers for similar disconnects between the data presented and the conclusions drawn.

THE URGENT NEED – AN INDEPENDENT COMMISSION OF ENQUIRY INTO THE WHI ACTIVITIES AND KEY PUBLICATIONS

There are two obvious and immediate actions to be called for:

(1) The FDA needs to activate an Advisory Committee to revisit the black-box warnings on postmenopausal hormones. Specifically, there needs to be a separation of the advisories for estrogen alone from estrogen and progestogen combined usage.
(2) The irresponsible approach taken by the NIH in reporting the data and their consistent failure to provide a comprehensive final analysis and overview now leaves little alternative but to call for an independent commission, free of conflicts of interest including with the NIH itself, to do precisely that. Even now, the key WHI investigators are behaving like the divorced husband who murders his ex-wife, and then claims child custody because his children have no mother. They have written a contrary response, challenging the NAMS 2012 HT Position Statement, that has been appropriately refuted by NAMS, being incorrect and illogical[2,18,19]. But it does further demonstrate the desire of the WHI investigators to control the indications for HT after menopause solely on the basis of the WHI publications and ignoring entirely the wealth of other published evidence, or that the WHI was never a study about menopause *per se*.

An independent commission of enquiry needs to be established without delay including at least appropriate representatives from women's health organizations, experts in the related health specialties, statisticians, key individuals from the WHI itself, and representatives from the leading journals like *JAMA* and the *New England Journal of Medicine*. The latter, *NEJM* and *JAMA*, are essential to provide transparency on the review process which the key papers received before publication. Both the WHI and *JAMA* are necessary to explain how 'almost nominally statistically significant' (meaning insignificant) findings in the results section of a paper could be converted into a recommendation for women to avoid postmenopausal hormone usage[2]. While it would appear that there may be a question of integrity with some of those involved in reporting WHI results, if a commission was created entirely independent of the FDA, NIH and the scientific journal representatives, their conclusions, however justified, would probably not be taken seriously. In the absence of general trust in the proposed commission, any conclusions published thereby would just add another chapter to an already acrimonious debate.

The proposed commission should scrutinize all the key WHI publications for adequacy of the methodology for the primary outcome in the question to be tested (e.g. measures of sexuality, or quality of life), and for consistency between the results reported in the body of the papers and the conclusions drawn. Ideally, there should be an investigation of the monitoring process that took place at the study sites during the course of the study. If irregularities or discrepancies are found between methodology, results and conclusions, these should be so listed. Where these exist, clarification should be provided on the peer-review process that allowed such papers to see the light of day. Then a comprehensive summary of the key WHI overall results should be brought together in a single white paper.

Women progressing through and beyond menopause in the next decade need to be spared the unnecessary harm inflicted on their sisters of the previous decade, as resulted from the rush to publication of incomplete and poorly analyzed data by the Women's Health Initiative spokespeople in July 2002.

Conflict of interest Professor Utian is not consulting or on any pharma speaker panels on ET/EPT/HT. He is consulting on non-hormonal products for the following companies: Hygeia, Chair Advisory Board (from 11.27.07), Bionovo (from 03.01.08), Cleveland Clinic Foundation Innovations Center (from December, 2009), Pharmavite, Chair Menopausal Health Advisory Board (from 11.24.10), Merck, Sharp & Dohme (from 01.23.11), Novogyne (from 02.15.11), Bayer FSD Advisory Board (from 03.01.11), Teva Women's Health Inc. (from 04.07.11), Pfizer Inc. (from 01.31.11 to 08.31.11).

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