

The Women's Health Initiative study and Hormone Therapy – what have we learned 10 years on?

International Menopause Society

Embargo: 00.01 Central European Summer time, Tues 22nd May, 2012

In July 2002 the publication of the first Women's Health Initiative (WHI) report caused a dramatic drop in Menopausal Hormone Therapy (HT) use throughout the world. Now a major reappraisal by international experts, published as a series of articles in the peer-reviewed journal *Climacteric* (the official journal of the International Menopause Society), shows how the evidence has changed over the last 10 years, and supports a return to a "rational use of HT, initiated near the menopause".

The reappraisal has been carried out by some of the world's leading experts in the field, including clinicians who worked on the original WHI study. Summarising the findings of the special issue, authors Robert Langer, JoAnn Manson, and Matthew Allison conclude that "classical use of HT" – MHT initiated near the menopause – will benefit most women who have indications including significant menopausal symptoms or osteoporosis.

Dr. Robert Langer, Principal Scientist at the Jackson Hole Center for Preventive Medicine, Jackson Wyoming, was the Principal Investigator of the WHI Clinical Center at the University of California, San Diego. He said

"With 10 years hindsight we can put the lessons learned from the WHI HT trials into perspective. In some ways we've come full circle – studies in recently menopausal women that suggested protection against major diseases led to testing whether that would carry over to older women who have even greater risks of heart attacks and fractures. That hope proved false. Unfortunately the results were wrongly generalized back to women like those who inspired the study. Information that has emerged over the last decade, shows that for most women starting treatment near the menopause, the benefits outweigh the risks, not just for relief of hot flashes, night sweats and vaginal dryness, but also for reducing the risks of heart disease and fractures".

Langer continued:

"Overgeneralizing the results from the women who were -- on average -- 12 years past menopause to all postmenopausal women has led to needless suffering and lost opportunities for many. Sadly, one of the lessons from the WHI is that starting HT 10 years or more after menopause may not be a good idea, so the women who were scared away by the WHI over this past decade may have lost the opportunity to obtain the potential benefits."

Professor JoAnn Manson (Harvard Medical School and Brigham and Women's Hospital, Boston, MA), who has been one of the WHI Principal Investigators since the study started, said:

"An important contribution of the WHI was to clarify that, for older women at high risk of cardiovascular disease, the risks of HT far outweighed the benefits. This halted the increasingly common clinical practice of prescribing HT to women who were far from the

onset of menopause. Unfortunately, these findings were extrapolated to newly menopausal and healthy women who actually had a favourable benefit: risk ratio with HT. The WHI results point the way towards treating each woman as an individual. There is no doubt that HT is not appropriate for every woman, but it may be appropriate for many women, and each individual woman needs to talk this over with her clinician”.

The authors note that the initial press reaction, following the lead of the WHI press release, over-emphasised a relatively small increase in breast cancer, so distorting the overall view of the report.

WHI researcher Professor Matthew Allison (University of California, San Diego), said:

“It is important to put the results of the WHI trials into context. That is, being obese, not exercising or excess alcohol consumption confer higher absolute risks for breast cancer than HT use.”

Note that a brief summary of the papers in this special issue of *Climacteric* appears below.

ENDS

This special issue, “The Women’s Health Initiative – a decade of progress” will appear in the June 2012 issue of *Climacteric* (vol 15, issue 3). This goes on line on 22nd May, at this URL: <http://informahealthcare.com/cmt>. *Climacteric* is the official journal of the International Menopause Society (IMS). The authors can be contacted as follows:

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ABSTRACT: *Have we come full circle-or moved forward? The Women’s Health Initiative 10 years on”, by R.D Langer, J.E Manson, and M.A. Allison, Climacteric Vol15 no 3 pp206-213*

In mid-summer 2002, the announcement that the Women’s Health Initiative (WHI) trial of combination hormone therapy (HRT) had stopped jolted the field of women’s health. It set off a cascade that first stunned, then meaningfully changed the future for millions of women, their partners, and tens of thousands of clinicians and scientists. With 10 years’ hindsight, we can begin to put the lessons learned from the WHI HRT trials into perspective. These trials were primarily designed to test whether women initiating HRT considerably past menopause, and mostly asymptomatic, experienced treatment benefits from HRT expected from studies of generally symptomatic women who started near menopause. The definitive answer was ‘no’. Unfortunately, the findings were generalized to all postmenopausal women regardless of age. Data accumulated from the WHI and other studies over the past decade have shown that, in women with symptoms or other indications, initiating HRT near menopause – the classic pattern of use – will probably provide a favourable benefit : risk ratio. Spurred by the WHI, many hypotheses and some insights about potential mechanisms for HRT effects on diverse organ systems have emerged, along with new perspectives on regimens, compounds, and routes of administration. This overview provides an historical perspective on the WHI design and the evolution of its message; summarizes current perspectives and insights contributed by eminent colleagues; reviews the state of the art; and looks to the future. We have come full circle in some ways, with mounting evidence supporting

benefit for HRT started near menopause and with hard lessons learned about pathophysiology, publicity and interpreting data. Now we move on.

Summary of papers

This special issue of *Climacteric* contains a series of articles reviewing the position of HRT, 10 years after the WHI. There is a wealth of information here, which is impossible to communicate in a single press statement. Here are simplified summaries of each article, *please refer to each individual article for more details.*

Quality of Life *The WHI study suggested that HRT use led to minimal improvement in quality of life (QoL). As the WHI study wasn't designed to look at women going through the menopause, it underestimated the real extent of effect of HRT on QoL. This has caused suffering to many women (Pines et al).*

HRT for Urogynecological and sexual health *Around 50% of postmenopausal women will suffer urogenital atrophy. Studies indicate that locally applied hormone therapy is generally more effective than systemic HRT for urogenital symptoms, including dyspareunia, which can be a critical determinant of a woman's interest in sex.(Nappi & Davis)*

Timing of HRT initiation, and cost effectiveness *The weight of evidence now supports a 'window-of-opportunity' for women taking HRT before the age of 60 and/or within 10 years of the menopause. This reduces the risk of coronary heart disease and overall mortality. HRT is more effective for this than other medicines such as statins and aspirin, and is cost-effective. Starting HRT later than this increases risks to women (Hodis et al).*

Stroke *There is a modest increase in stroke risk with HRT use if started near the menopause. This risk rises considerably in women who start at older ages. There is some evidence that use of HRT patches (as opposed to pills) may not increase stroke risk, but this needs to be confirmed (Henderson and Lobo).*

Venous Thromboembolism *There is an increased risk of venous thromboembolism with oral HRT. This may be increased with age and obesity, and may vary by the progestogen used. Observational studies suggest that it may not be associated with transdermal HRTs (patches), but this needs confirmation (Archer and Ogar).*

Breast cancer *There is an increase in breast cancer with E+P HRT, but this is small. It has also been exaggerated by press reports, causing fear in many women. They conclude that large numbers of women with substantial menopausal symptoms and low breast cancer risk will benefit from HRT use (Gompel and Santen).*

Colorectal Cancer *This is the second most common cancer in women (after breast cancer). Evidence from the WHI and other trials suggests that current HRT users have a 40% reduction in colorectal cancers. The authors say that it is too early to consider HRT use in the prevention of colon cancer (Barnes and Long)*

Dementia Initial WHI results showed an increase in dementia for both E+P and E alone users. This review including recent publications from other studies suggests that this may be influenced by the timing of the HRT initiation, with benefits for those starting nearer the menopause, but increased risks for women starting at older ages (Maki and Henderson).

Fractures The WHI "Global Index", which looked at the balance of risks and benefits, inappropriately downgraded the importance of fractures. The authors argue for a more rounded view. They say that that HRT gives more bone benefits than many other drugs (e.g. bisphosphonates), and so restrictions on HRT use as a first-line therapy are not appropriate (de Villiers and Stevenson)

Overall effects of the drop in HRT use This is difficult to gauge, because data varies from country to country. In one large study HRT discontinuation led to a 55% increase in fractures after 6.5 years. There was also a small drop in breast cancers after the drop in use in HRT, most notably in the US, but not seen in all countries, that was consistent with an effect on existing tumours. HRT discontinuation may lead to an increase in cardiovascular disease, but given the long lag time for cardiovascular events this would take substantial time to become apparent (Burger et al)

The WHI and media The author suggests that the WHI's dramatic presentation of the initial findings set the subsequent tone for the way that the media came to view the HRT issue (Simon Brown).