



INTERNATIONAL MENOPAUSE SOCIETY

**HRT in the early menopause:  
scientific evidence and common perceptions**

Summary of the First IMS Global Summit on menopause-related issues

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**INTRODUCTION**

Hormone replacement therapy (HRT) remains the first-line and most effective treatment for menopausal symptoms. But, despite massive, good-quality clinical outcome data on efficacy and safety when HRT is begun for symptoms in the early postmenopause, many physicians and lay people believe that hormones are risky and undesired even in the most appropriate case scenarios. Many misconceptions and misperceptions play roles in this complicated situation: some are purely scientific, others are cultural or social. The importance of the media and internet as effective, but unmonitored, means for dissemination of information, interpretation and recommendations cannot be ignored. Actual scientific facts and data have become trivialized in the mass media, often receiving less editorial scrutiny than normal journalism. Furthermore, many HRT prescribers and users do not attempt to broaden their knowledge on menopause and its treatment beyond capturing headlines or short commentaries, often produced by unqualified or prejudiced sources or unprofessional people.

As a result, a gap has formed between the actual clinical evidence and the way it is perceived by all concerned.

The results of the Women's Health Initiative (WHI), a very large, government-sponsored study of hormone treatment regardless of indications (in contradistinction to normal practice that is based on clinical symptoms and signs), were prematurely released before the study was completed and before the results could be properly evaluated. As a result, the results were over-interpreted and negatively slanted. It was viewed as a negative study by its investigators and failed to emphasize the data, which pointed at the vast importance of age and time since menopause as major determinants of the benefit–risk equilibrium of HRT and the many benefits from timely employment of HRT. This was a catalyst for negative sentiments toward HRT. By the time that more detailed analyses from the WHI study could be published in the past 2 years, much ground was lost for all concerned and much remains to be set right for patients and caregivers, alike. At present, it is clear that the WHI showed that properly timed HRT is safe for healthy women in their early postmenopause and has major preventative effects against fractures. It reduces mortality and this may be, in large part, due to prevention of heart disease.

The premature evaluation of the WHI includes statements and warnings from many health authorities, such as the US Preventive Services Task Force (USPSTF) and the European Agency for the Evaluation of Medicinal Products (EMA) that sent a message that still prevails: the use of HRT is dangerous and therefore should be avoided, unless there is a substantial reduction in quality of life because of menopausal symptoms, in which case treatment should be given for the shortest possible duration. This seems untenable in light of the presently available data, the opinion of skilled and experienced health professionals, and even some of the WHI investigators themselves.

The aim of the International Menopause Society (IMS) in developing the Zürich Summit was to openly discuss and better understand the current situation in various areas of the globe. The knowledge and perspectives of scientists, consumers and the media were sought to recommend ways to narrow the gap between the evidence and its perception by health professionals and the lay public. The forum, which included experts from the various fields of menopause medicine and representatives of 40 national and regional menopause societies, agreed that the following summary of the scientific data will be addressed as the 'Evidence'. Each statement will quote its scientific level of evidence, and a list of the corresponding

references is attached at the end of the document. Level A evidence refers to data from randomized controlled trials, whereas Level B evidence comes from case–control/observational studies. As pointed out in the Summit’s title, the focus of discussions was the effects of HRT first administered during the early postmenopausal period.

## **QUALITY OF LIFE AND MENOPAUSE**

The perception of menopause and its impact on quality of life vary in different areas of the world<sup>1-5</sup>. In some places, menopause leads to a higher social status, in others – not. The forum agreed that the issue of quality of life is pivotal for any discussion on menopause management and the evaluation of the benefits versus the risks of HRT. Quality of life may be defined in many ways, based on medical, cultural and social parameters, but is largely subjective and therefore not easy to evaluate under a global, unified scale. Some may say that menopause is just a physiological stage during a woman’s life cycle and therefore its associated adverse consequences of quality of life should not be medicalized. Others may argue that the risks of HRT do not justify its use unless quality of life is substantially compromised. The negative sentiments coming from the WHI publications and the related media coverage intimidate women and health-care providers and in a way lead to confusion and to a degraded credibility of the medical profession over these issues, but the WHI Quality of Life analysis started with only 11% of subjects who had moderate or severe hot flushes and did not have the power to determine a comparative improvement in the treatment vs. placebo group<sup>6</sup>. Such a low incidence of climacteric symptoms is not representative of the healthy peri- and early postmenopausal women treated in everyday practice.

- In symptomatic postmenopausal women, quality of life and sexuality are improved by HRT<sup>7,8</sup> and, in the presence of symptoms of androgen deficiency, by additional androgen administration.
- In some cultures, and for some women, vaginal bleedings are unacceptable<sup>4</sup>; if bleeding cannot be eliminated, alternatives to HRT may be used.
- There is no evidence that so-called ‘natural’ products and unregulated hormone products (compounded bio-identical) significantly improve quality of life.

## PERCEPTIONS VS. SCIENTIFIC DATA (THE 'EVIDENCE')

### HRT, coronary heart disease, stroke and thromboembolism

#### *Perceptions*

- HRT increases coronary heart disease (CHD) risk throughout the whole postmenopausal period.
- HRT causes an increase in coronary events in the first 1–2 years in all women.
- Stroke risk is substantially increased in women receiving HRT.
- The risk of both venous and arterial thromboembolism is increased during HRT.

#### *The evidence*

- HRT in women aged 50–59 years does not increase CHD risk in healthy women and may even decrease the risk in this age group<sup>9</sup>. [A]
- Estrogen-alone therapy in the age group 50–59 was associated with significantly less coronary calcification (equivalent to a smaller plaque burden), which is consistent with findings of a lower coronary intervention score in women of this age in the WHI study<sup>10</sup>. [A]
- Early harm (more coronary events during the first 2 years of HRT) was not observed in the early postmenopausal period. The number of CHD events decreased with duration of HRT in both WHI clinical trials<sup>11</sup>. [A]
- Data derived from randomized controlled trials in the age group 50–59 are similar to the older observational data suggesting a protective effect of HRT on coronary disease<sup>9,12</sup>. [A, B]
- It is unclear at present whether there is a statistical increase in ischemic stroke with standard HRT in healthy women aged 50–59. The WHI data showed no statistically significant increase in risk; nevertheless, even if statistically increased, as found in the Nurses' Health Study, the low prevalence of this occurrence in this age group makes the attributable risk extremely small<sup>13,14</sup>. [A,B]
- The risk of venous thrombosis is approximately two-fold higher with standard doses of oral HRT, but is a rare event in that the background prevalence is extremely low in a healthy woman under 60 years of age<sup>15</sup>. [A]
- The risk of venous thrombosis is possibly less with transdermal, compared with oral estrogen therapy<sup>16</sup>. [B]

## **Breast**

### *Perceptions*

- All types of HRT cause an increased risk of breast cancer within a short duration of use.
- HRT causes an increase in mortality from breast cancer.
- The reported decline in breast cancer rates in the US following the publication of the WHI proves that HRT causes cancer.
- HRT causes an increase in mammographic breast density.
- Increase in mammographic breast density is associated with an increased risk of breast cancer.

### *The evidence*

- There is a wide variation across the world in the incidence of breast cancer and its risk factors<sup>17</sup>.
- There are multiple risk factors for breast cancer, including life-style factors especially alcohol intake, obesity and lack of exercise. These need to be included during counselling to put the magnitude of risk of HRT into an appropriate perspective<sup>18,19</sup>. [B]
- After 5 years' use of combined estrogen and progestogen, there is a small increase in risk of breast cancer in North American women of about eight extra cases per 10,000 women per year. However, no significant increase was seen in women without prior use of HRT in the WHI study<sup>20</sup>. [A]
- Estrogen-only use does not cause an increase in breast cancer for up to 7 years<sup>21</sup>. [A] In observational studies, a small increase in the risk with estrogen-alone therapy appears with long-term use<sup>22</sup>. [B]
- Women using combined HRT before a diagnosis of breast cancer have a reduced mortality<sup>23</sup>. [B]
- A decline in the incidence of breast cancer in the USA started before the WHI publication and can be partially related to fluctuation in screening<sup>24</sup>. There has been no decline in breast cancer registration in the UK following the Million Women Study report, nor in Norway, Canada, the Netherlands and countries with stable screening programmes<sup>25</sup>. [B]

- Combined estrogen and progestogen therapy may cause increased breast density in up to 50% of postmenopausal women, dependent on the regimen (dosage, type of progestogen). The effect of estrogen alone is smaller<sup>26</sup>. [A]
- The effect on breast density is dose-related. Ultra-low-dose regimens do not cause any perceptible change in density<sup>27</sup>. [A]
- The average increase in breast density under standard-dose HRT is only about 5–10%<sup>28</sup>. [A]
- Increased baseline breast density is a risk factor for breast cancer<sup>29</sup>. There are no data to support a direct association between HRT-induced breast density changes and the risk of developing breast cancer.
- Many women who develop breast cancer have no known risk factors other than growing older and most women with known risk factors do not develop breast cancer.
- Individual risk analysis for breast cancer is strongly recommended in clinical practice<sup>30</sup>.

## **Bone**

### *Perceptions*

- HRT should not be used for bone protection because of its unfavorable safety profile.
- HRT is not as effective in reducing fracture risk as other products, e.g. bisphosphonates.
- Official recommendations by health authorities (EMA, FDA) limit the use of HRT to a second-line alternative. HRT could only be considered when other medications failed, were contra-indicated or not tolerated or in symptomatic women.

### *The evidence*

- Overall, HRT is effective in the prevention of all osteoporosis-related fractures, even in patients at low risk of fracture<sup>31,32</sup>. [A]
- Although no head-to-head studies have compared HRT to bisphosphonates in terms of fracture reduction, there is no evidence to suggest that bisphosphonates or any other antiresorptive therapy are superior to HRT.

- It is therefore suggested that, in 50–59-year-old postmenopausal women, HRT is a cost-effective first-line treatment in the prevention of osteoporotic fractures.
- Even lower than standard-dose preparations maintain a positive influence on bone indices such as bone mineral density<sup>33</sup>. [A]
- HRT has a positive effect on osteoarthritis and the integrity of intervertebral disks.

## **Cognition**

### *Perceptions*

- Menopause transition is associated with cognitive decline.
- HRT increases the risk of cognitive/memory impairment and dementia at any age.
- Progestogens counteract estrogen effects in the brain.

### *The evidence*

- At present, there is no evidence of substantial cognitive decline across the menopausal transition<sup>34</sup>. [A] However, many women experience cognitive difficulties in association with vasomotor symptoms, sleep disturbances and mood changes<sup>35,36</sup>.
- Verbal memory performance relates with the objective number of hot flashes women experience but not to the number of hot flashes they report<sup>35</sup>.
- Clinical trial findings currently find no cognitive benefit among women initiating HRT late in the postmenopausal period (i.e. after age 65)<sup>37</sup>.
- Cognitive benefits from estrogen replacement therapy appear to depend on age of initiation<sup>38</sup>.
- Observational studies show a decreased risk of Alzheimer's disease in hormone users and typically involve women who initiated estrogen therapy early in the menopausal transition<sup>39-41</sup>. [B]
- Limited data exist on the effect of progestogen added to estrogen in the early postmenopause period. Clinical trial data suggest no cognitive benefit with MPA early in the menopause<sup>42</sup>. [A]

## **ACTIONS TO BE TAKEN**

The forum agreed that education and dissemination of the clinical data are crucial in the process of closing the gap between the scientific evidence on HRT and its

perception. Three main targets were identified: the health-care providers, the consumers and the journalists. The forum did not believe that actions should be taken vis-à-vis the regulatory/health authorities, since the chance of changing their opinion at this moment is slim. In order to avoid any debate over the 'Evidence', it was based entirely on high-quality information, derived from randomized clinical trials whenever possible. Through presentations from each continent, it became quite clear that menopause symptoms and the incidence of illnesses associated with menopause or HRT may vary to a large extent in different parts of the world, as well as priorities in medical care. In addition, cultural and social attitudes may have a substantial impact, all affecting perceptions and decision-making in regard to menopause management and the use of hormones. Therefore, each regional/national menopause society should adapt the general framework according to its local situation and needs. The message to be delivered should be simple and clear, stressing the benefits of HRT and relieving fears according to the best quality clinical evidence. The most frequent misperceptions should therefore be identified and balanced by the corresponding data that were published in the medical literature. The above bullet points may serve as a template to be used locally by the societies.

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