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EDITORIAL

A call to increase the use of hormone therapy to prevent disease in symptomatic postmenopausal women

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Current clinical guidelines for menopause hormone therapy (HT), including the 2017 North American Menopause Society (NAMS) position statement, recommend HT for symptom control and disease prevention for symptomatic women under age 50.[1] Unfortunately, since the Women's Health Initiative (WHI) report in 2002 the decline in use of HT has been precipitous and only about 5% to 6% of these women are current users.[2] This means that millions of women who could be safely treated hormonally are not and as a result have:

- menopause symptoms affecting their quality of life;
- adverse effects on the cardiovascular system, bone, mood, sexual health, and cognition; and
- increased risk of dying before age 70.

A recent *Menopause* editorial by Professor Amos Pines likened the impact of the 2002 WHI report to a ''shockwave'' which has led to avoidance of HT by younger symptomatic postmenopausal women.[3] In a new paper in this issue of *Menopause*, investigators echo Professor Pines in specifically expressing concern about the ''large declines in HT use in subgroups for whom HT is often recommended (for reducing CVD risk and other diseases) i.e. younger women and those with vasomotor symptoms (VMS).''[4] The data are from the Study of Women's Health Across the Nation (SWAN).

The SWAN investigators measured rates and determinants of the decline in use of HT, before and after the 2002 WHI report. Factors affecting HT initiation and continuance before and after the WHI 2002 report include media, provider advice, and opinions about HT from family and friends. Media impact is seen as a negligible factor influencing HT continuance pre-WHI but becomes the major factor triggering discontinuance of HT afterward. Before 2002, 29% to 41% of women who initiated HT did so for prevention of heart disease (cardiovascular disease [CVD]) and/or osteoporosis. After 2002, 2% to 10% initiated HT for these reasons. Provider advice changed from being pro-HT to being against it for disease prevention. Friends and relatives who used HT and supported using HT before 2002 seem to have disappeared along with conversation in general about menopause and hormones. Of note, 25% of the women discontinued HT because they did not like taking it before and after 2002.

It is important to remember that at least 2/3 of all symptomatic postmenopausal women are under age 50. One out of three of these women are surgically menopausal and another 1/3 are naturally menopausal by age 50. The surgically menopausal women are significantly younger with about half under age 45. These women experience moderate-to-severe VMS with greater frequency (90% vs 70%) and they are more likely to develop osteoporosis, CVD, and a dozen or more other diseases.[5,6] In the WHI estrogen-alone (ET) versus placebo trial, 83% of the cohort of 1,673 women aged 50 to 59 had hysterectomies by age 49 or younger.[7]

DISEASE PREVENTION IS A ''CORE'' ISSUE IN THIS DEBATE

The WHI studies were developed to determine whether or not HT prevents CVD and mortality. The new SWAN report indicates that disease prevention was a driving force for doctors to prescribe and for women to use HT before the initial WHI report. Unfortunately, misinterpretation of the WHI data took the rug out from under this position. The result has been that prescribers and consumers have come to perceive HT to be only a symptom-control therapy with menopause symptoms not taken very seriously. On the contrary, menopause symptoms should be taken seriously as pathophysiological changes associated with VMS contribute to disease processes including:

- a higher incidence of insulin resistance and elevated glucose levels, greater intima media thickness, and an impairment of arterial endothelial response[8];
- increase in white hyperintensities in the brain, an indicator of neuronal damage[9];
- increased rates of bone loss[10]; and
- cognitive decline with Alzheimer pathology.[11]

Also to be taken seriously are the health benefits seen when symptomatic women initiate HT before age 50 and/or within 10 years of menopause. These include reduced risks for CVD, osteoporosis, cognitive decline, vulvovaginal atrophy, and dyspareunia.[5,12,13] Fear of developing breast cancer should

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be allayed by the WHI findings that ET actually reduces risk for developing and dying from breast cancer.[14] Other studies indicate that use of ET or E+progestogen therapy in younger postmenopausal women, including high-risk women after risk-reduction bilateral oophorectomy, does not increase risk for developing breast cancer.[15,16]

Significantly reduced risk for early mortality is seen in meta-analyses of the literature concerned with HT use in younger women.[17,18] In the WHI ET study women aged 50 to 59 receiving ET versus placebo show reduced mortality rates for CVD, breast cancer, and Alzheimer's disease.[19,20] Unfortunately, lack of awareness of these findings continues to lead to avoidance of HT including ET after hysterectomy resulting in unwarranted mortality in these women prior to age 70.[21]

CHANGING BEHAVIOR TO MOVE FORWARD WITH THE USE OF HT

There are many barriers to increasing use of HT including:

- inadequate menopause education and training of medical professionals;
- medical society guidelines which do not recognize the benefits of HT or may even recommend against it even when HT is warranted;
- frightening ratings from governmental agencies such as the Food and Drug Administration (FDA) Black Box for estrogen-containing preparations and the ''D'' rating from the US Preventative Services Task Force for hormonal treatment in older women;
- costs for hormone prescriptions;
- insurance company denial of coverage for menopause health care and hormone prescriptions;
- the absence of major pharmaceutical companies which had, before 2002, supported basic research, development of new drugs, Continuing Medical Education events for professionals, and promotion of menopause care for women consumers;
- competition from commercial interests which promote alternative non-FDA-approved therapies and debunk approved HT; and
- misinformation on the Internet.

Of all the barriers to progress in disseminating positive data, silence about anything to do with menopause may well be the most challenging. For 15 years or more, menopause has been almost absent from the agenda for medical school curricula, resident training, grand rounds, and other CME activities. Outside medicine, positive findings about menopause HT have been barely reported in the popular media.

But there are signs that we may have entered into a time of change in attitudes and behavior affecting HT use. Recently, media including the *New York Times* and the *Los Angeles Times* have printed a number of positive articles reporting benefits of HT. For example, see ''Once and for all: Hormone replacement is good for women'' in the *Los Angeles Times* on January 31, 2019. An important article published in 2016 in the *New England Journal of Medicine* titled ''Getting Clinical Care Back on Track'' is a call to arms.[22] It highlights the need to bring menopause education into primary care and OB/GYN residencies. Taylor et al[23] reported that physicians who become knowledgeable about published HT trials are more likely to prescribe it. At the October 2018 NAMS meeting, findings from a national cross-sectional survey indicated a significant number of young physicians, mostly women OB/GYNs, are interested in menopause and are motivated to give quality menopause care.[24] The 2017 NAMS Position Statement is an excellent tool for breaking the silence about HT and stimulating dialogue among providers as well as women consumers.

For the past 4 years, a small group, mostly made up of NAMS members, has forged an independent effort to stimulate interest in and understanding of menopause health care. We have taken a ''niche'' approach by focusing on ET therapy for women after hysterectomy. We chose this focus because ET after hysterectomy is the least controversial of menopause hormone therapies and is relatively easy to understand. ET is the only therapy that controls symptoms and reduces disease risks and mortality rates. The data for reducing breast cancer risk and mortality with ET has proved very helpful in reaching out to women consumers and professional audiences. Because our target population is younger postmenopausal women, we have been advocates for the use of ET for primary prevention of CVD. Through publications in refereed journals and presentations at grand rounds, regional and national meetings, and symposia for women and for professionals, we think we are helping others to learn about and rethink menopause and HT. Through an Internet site, empowher.com/ahah, millions of women who regularly go to this site are, hopefully, learning about ET, HT, and menopause health care.

The experiences of our group indicate that there has been a shift in attitudes toward HT among women and professionals. Noninterest seems to be yielding to growing interest, while negativity seems to be shifting to neutrality and even the beginnings of receptivity. The current generation of women reaching menopause was not traumatized by the media's scary take on HT in 2002. The data accumulated, especially in the last 5 years, indicating that ET actually decreases breast cancer risk and mortality, is very powerful. Other findings that confirm HT safety, symptom control, and disease prevention are impressive. New FDA-approved hormonal treatment options increase the potential for tailoring treatment to the individual and meeting with greater patient acceptance. We are optimistic about reaching a new generation of healthcare providers and women.

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